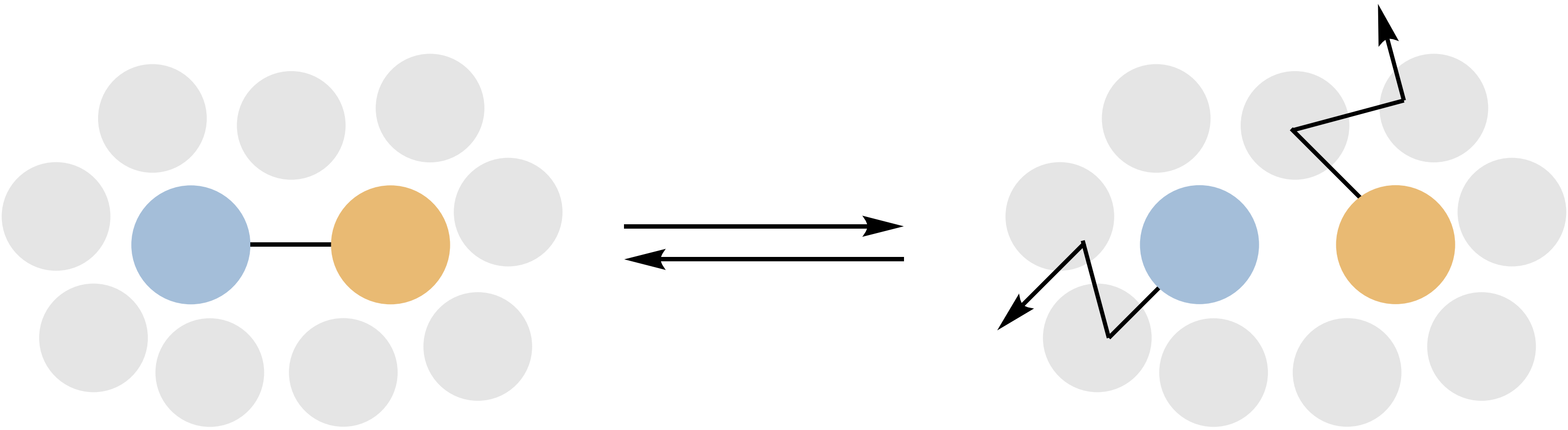
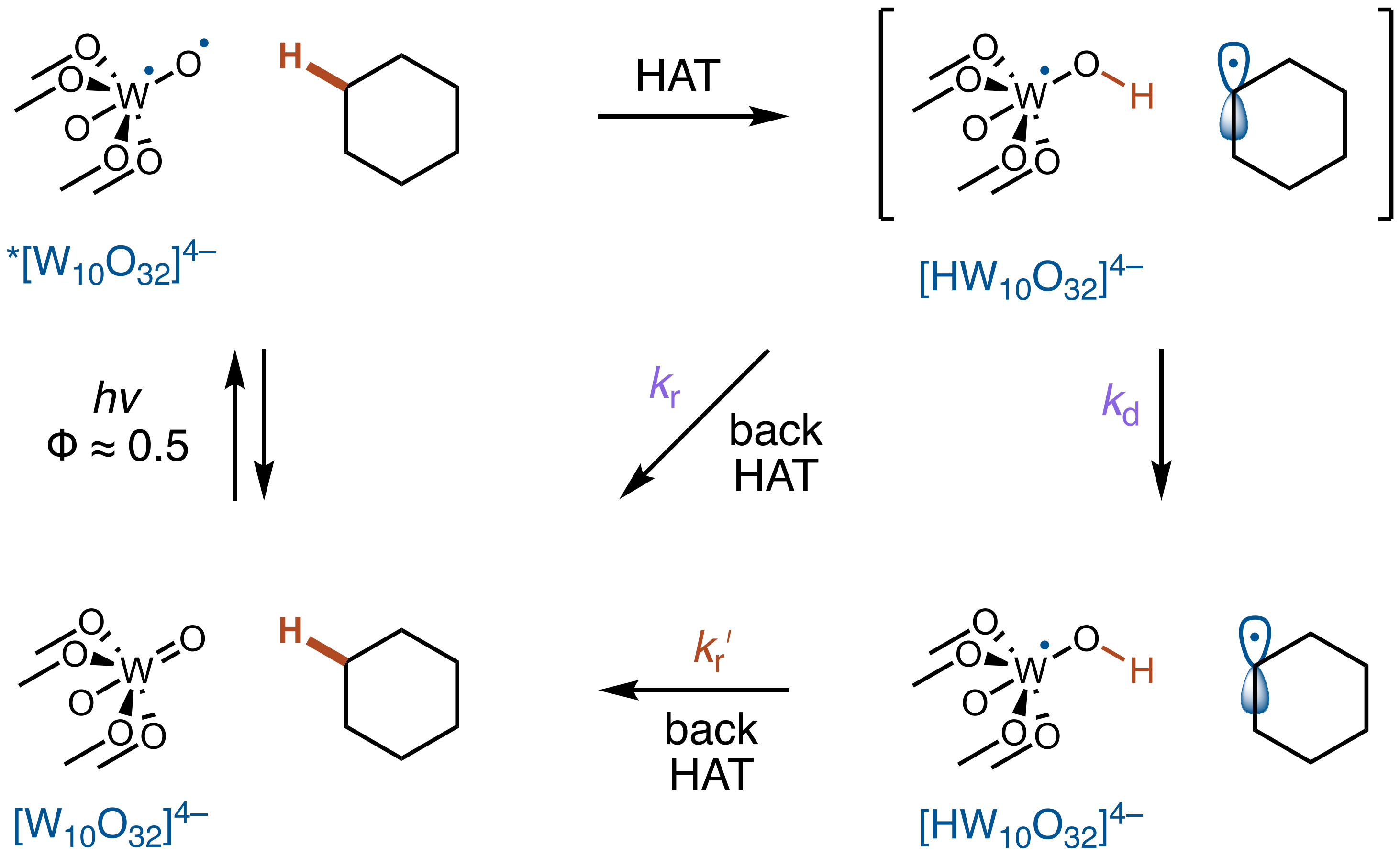
Radical Cage Effects



Patrick Sarver
MacMillan Group Meeting
22 April 2020

A problem that has bugged me for a while…



$^*[W_{10}O_{32}]^{4-}$

HAT

$[HW_{10}O_{32}]^{4-}$

$D_{C-H} \approx 100$ kcal/mol

$D_{O-H} \approx 30$ kcal/mol
(Bordwell equation)

hν
$\Phi \approx 0.5$

k_r back HAT

k_d

$[W_{10}O_{32}]^{4-}$

k_r' back HAT

$[HW_{10}O_{32}]^{4-}$

$\Phi_{lim} = 0.46$

free radicals

From transient absorption spectroscopy:

$k_r/(k_r + k_d) = 0.930$

almost every generated radical pair separates

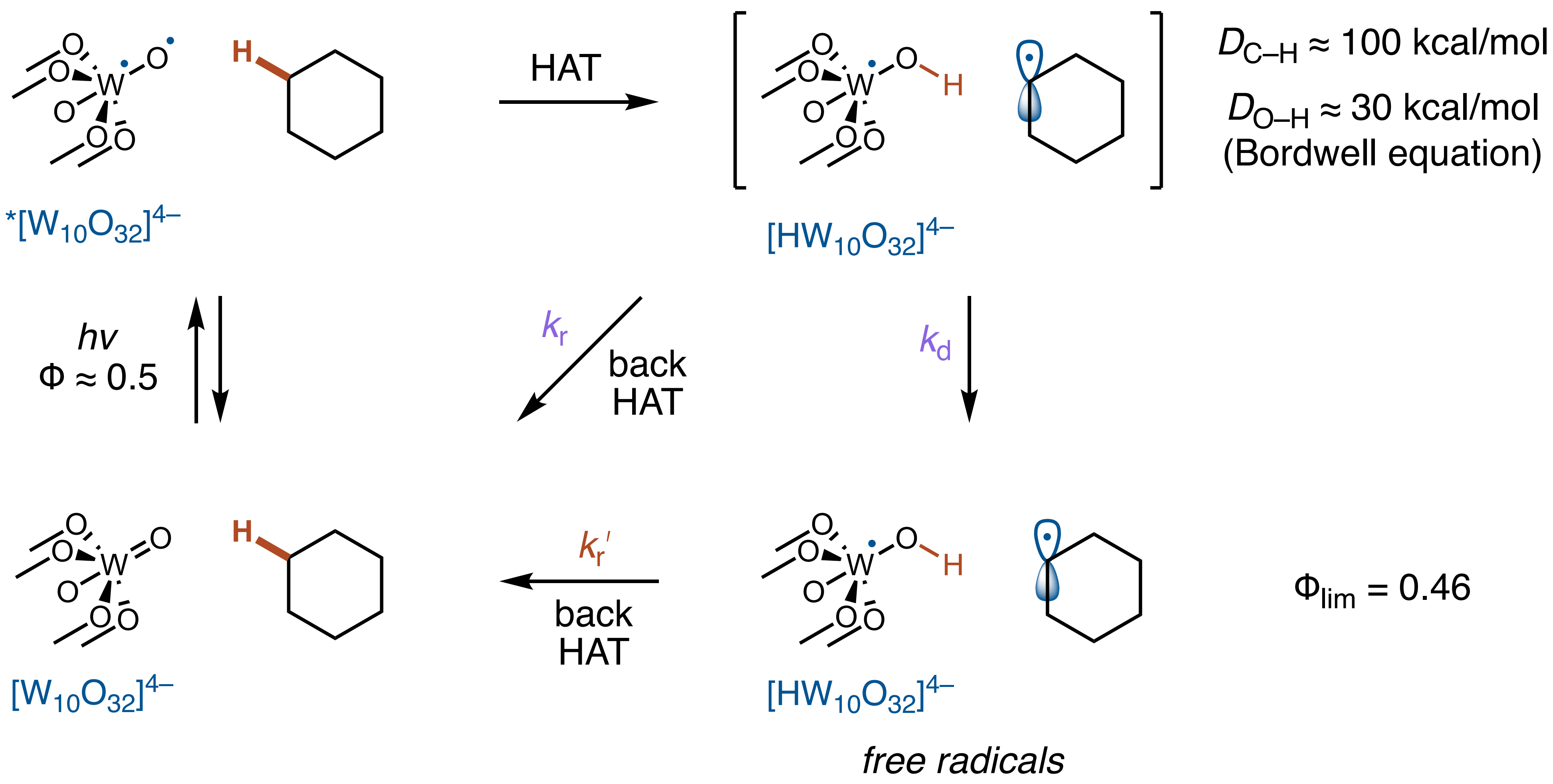
From competition with electrophilic alkenes:

$k_r' = 8 \cdot 10^9$

but recombination is diffusion limited!!

Duncan, D. C.; Fox, M. A. *J. Phys. Chem. A* **1998**, *102*, 4559–4567.
Dondi, D.; Fagnoni, M.; Albini, A. *Chem. Eur. J.* **2006**, *12*, 4153–4163.

A problem that has bugged me for a while…



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(Bordwell equation)

$h\nu$

$\Phi \approx 0.5$

k_r

back HAT

k_d

$[W_{10}O_{32}]^{4-}$

k_r'

back HAT

$[HW_{10}O_{32}]^{4-}$

free radicals

$\Phi_{lim} = 0.46$

Why is back HAT such a minor pathway?

Duncan, D. C.; Fox, M. A. *J. Phys. Chem. A* **1998**, *102*, 4559–4567.

Dondi, D.; Fagnoni, M.; Albini, A. *Chem. Eur. J.* **2006**, *12*, 4153–4163.

Outline

- **Introduction to cage effects**
  - *General definition, theoretical predictions*
- **Experimental support for the existence of cage effects**
  - *Quantum yields, product ratios as a function of reaction medium*
- **Parameters determining the magnitude of cage effects**
  - *Viscosity, reaction energetics, spin state, radical size, initial separation*
- **Recent case studies**
  - *Presence in biorelevant systems, transient absorption studies*

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Definition of radical cage effects

radicals are (almost) always generated in pairs

↓

if generated close together, they can react before diffusing apart

↓

radical cage effect:

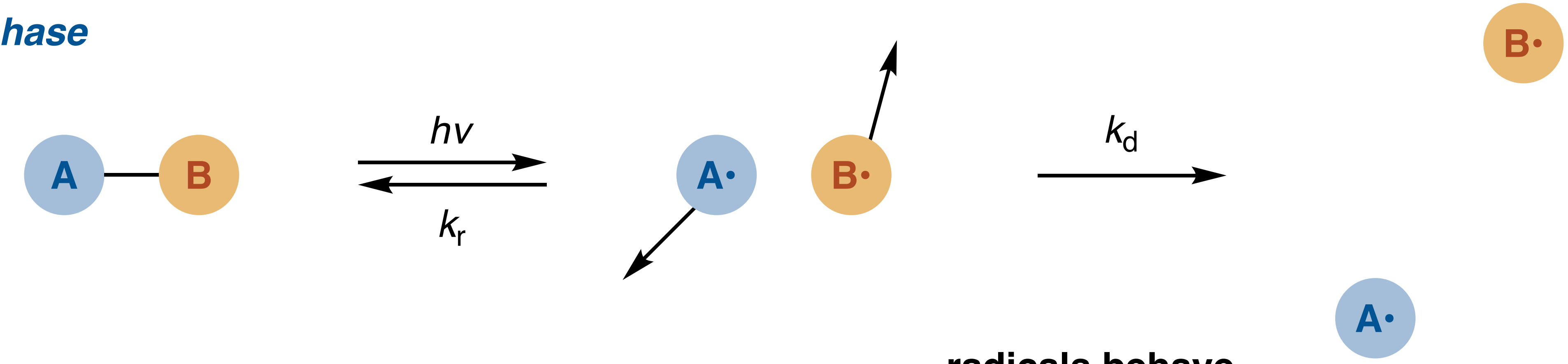
increased likelihood that diffusive separation will be slower than radical pair recombination in solution

Lorand, J. P. The Cage Effect. In *Progress in Inorganic Chemistry*; Edwards, J. O., Ed.; Wiley: New York, 1972; Vol. 17.
Koenig, T.; Fischer, H. “Cage” Effects. In *Free Radicals*; Kochi, J., Ed.; Wiley: New York, 1973; Vol. 1.

Introduction to "cage" effects

- Pairs of radicals generated in the gas phase rapidly separate

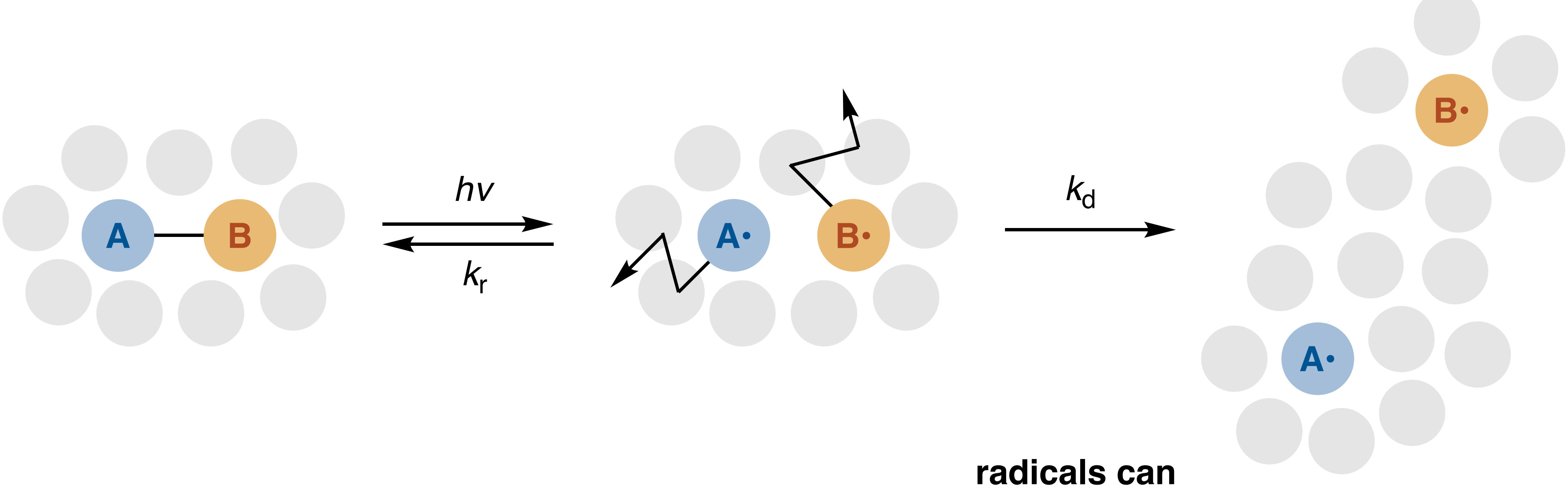
gas phase



low barrier to diffusion ⇒ $k_d >> k_r$ ⇒ **radicals behave "normally"**

- Pairs of radicals generated in solution must break through surrounding solvent to diffuse apart

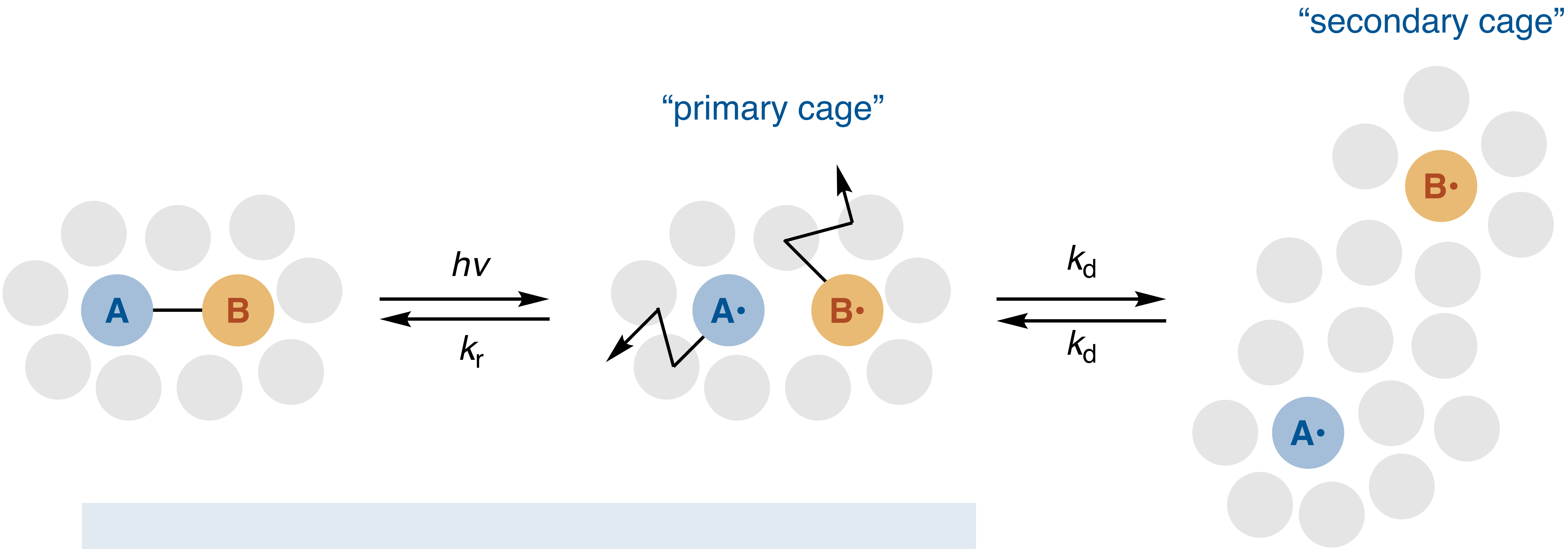
solution phase

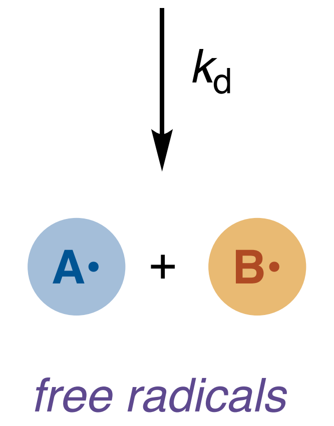


high barrier to diffusion ⇒ $k_r \approx k_d$ ⇒ **radicals can recombine before diffusing apart**

Introduction to “cage” effects

- Radicals that have broken free of the initial cage can diffuse back together





in most cases, no distinction is made between primary and secondary cage effects

$$F_{cP} = \frac{k_r}{k_r + k_d}$$

fraction of radicals that react in-cage

k_r = rate of recombination of radical pair

k_d = rate of diffusion of resulting radicals

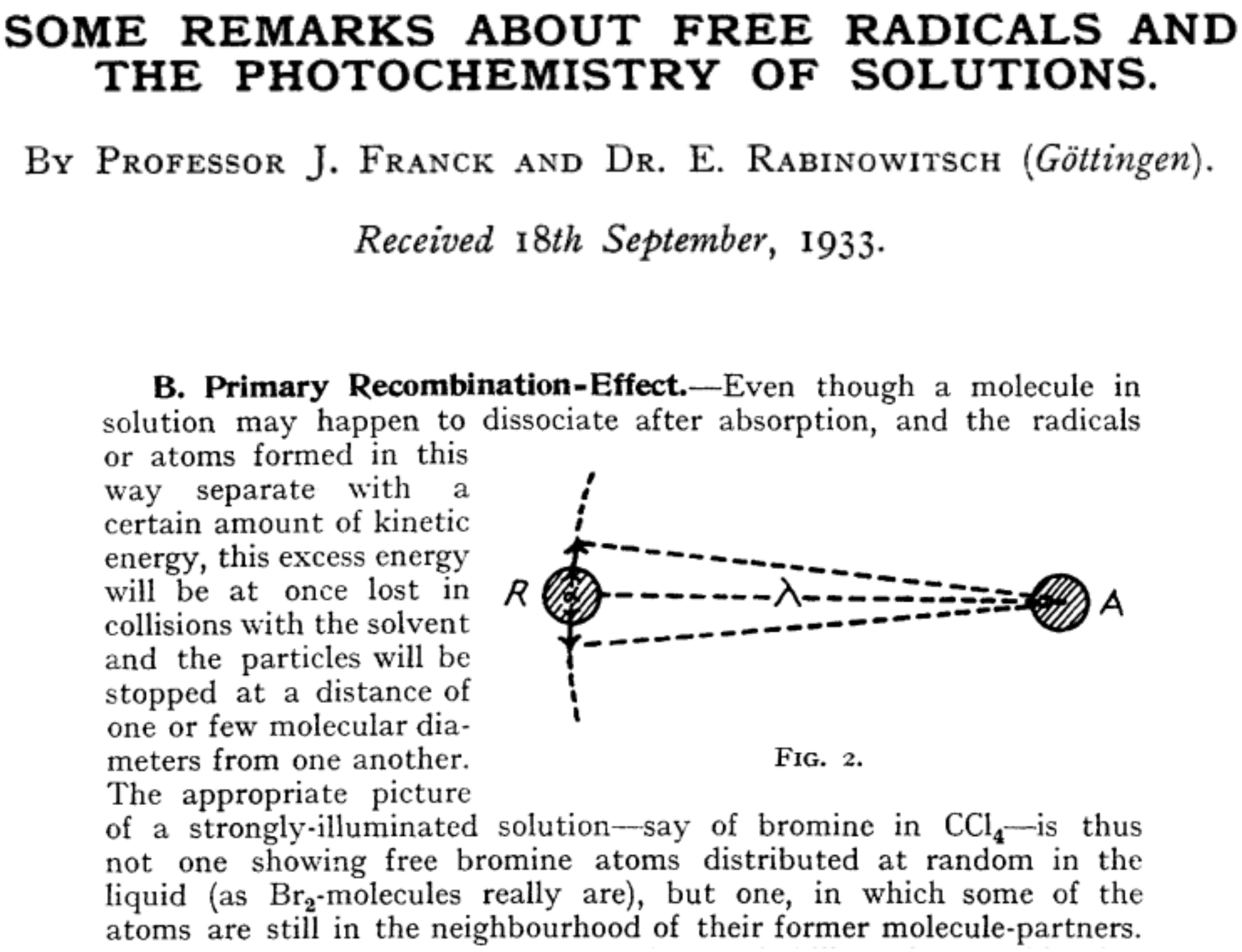
First report of "primary recombination effect"

- First prediction of differences between gas-phase and solution-phase radical recombination

James Franck.

17 April 1933 – becomes first German academic to resign in protest of laws excluding Germans of Jewish descent from government positions, published resignation in national press

November 1933 – moves to Johns Hopkins



SOME REMARKS ABOUT FREE RADICALS AND THE PHOTOCHEMISTRY OF SOLUTIONS.

By Professor J. Franck and Dr. E. Rabinowitsch (*Göttingen*).

Received 18*th September*, 1933.

B. Primary Recombination-Effect.—Even though a molecule in solution may happen to dissociate after absorption, and the radicals or atoms formed in this way separate with a certain amount of kinetic energy, this excess energy will be at once lost in collisions with the solvent and the particles will be stopped at a distance of one or few molecular diameters from one another. The appropriate picture of a strongly-illuminated solution—say of bromine in CCl_4—is thus not one showing free bromine atoms distributed at random in the liquid (as Br_2-molecules really are), but one, in which some of the atoms are still in the neighbourhood of their former molecule-partners.

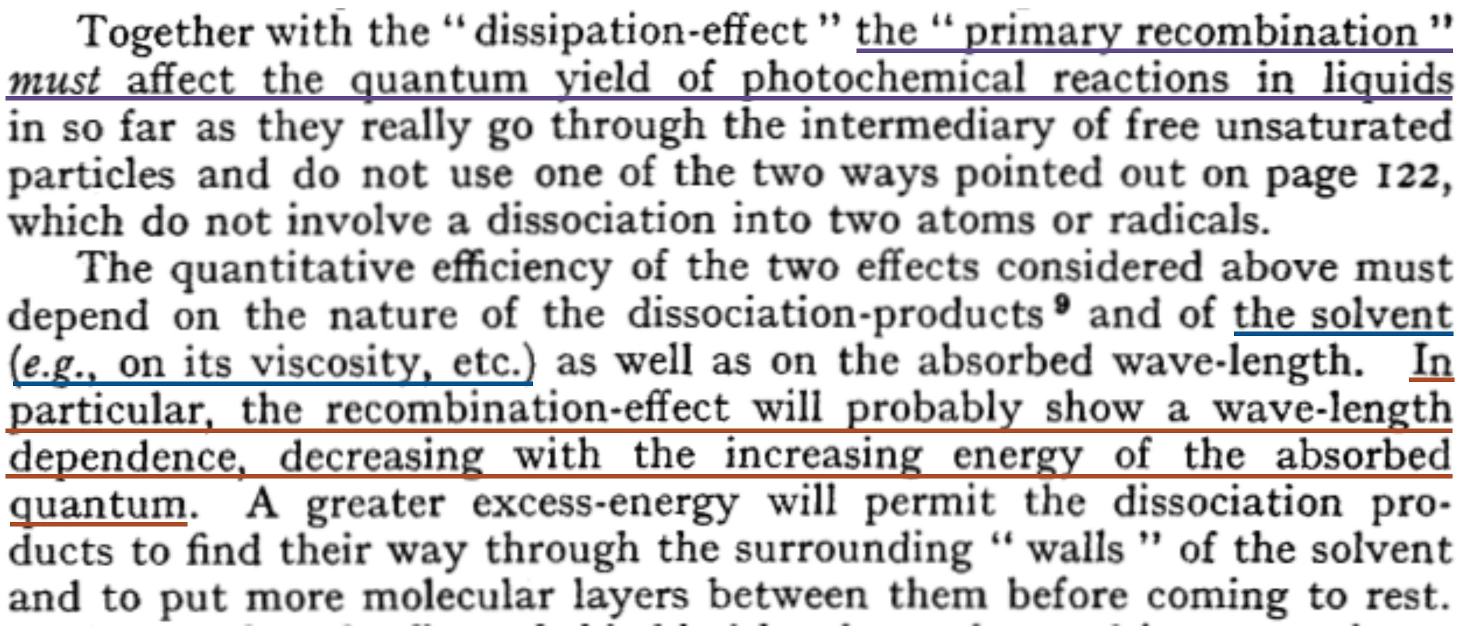
Fig. 2.

recognized that molecular dissociation in solution would not result in a random distribution of radicals

Franck, J.; Rabinowitsch, E. *Trans. Faraday Soc.* **1934**, *30*, 120–130

Prediction of parameters that determine magnitufe of cage effects

- Franck and Rabinowitsch predict many of the effects that determine “cage efficiency”



Together with the “ dissipation-effect ” the “ primary recombination ” *must* affect the quantum yield of photochemical reactions in liquids in so far as they really go through the intermediary of free unsaturated particles and do not use one of the two ways pointed out on page 122, which do not involve a dissociation into two atoms or radicals.

The quantitative efficiency of the two effects considered above must depend on the nature of the dissociation-products[9] and of the solvent (*e.g.*, on its viscosity, etc.) as well as on the absorbed wave-length. In particular, the recombination-effect will probably show a wave-length dependence, decreasing with the increasing energy of the absorbed quantum. A greater excess-energy will permit the dissociation products to find their way through the surrounding “ walls ” of the solvent and to put more molecular layers between them before coming to rest.

different observed quantum yield in solution vs. gas phase

viscosity dependence of cage effect magnitude

wavelength dependence due to role of excess energy in facilitating cage escape

all of these predictions were later experimentally validated

Franck, J.; Rabinowitsch, E. *Trans. Faraday Soc.* **1934**, *30*, 120–130

Early "experimental" support for cage effects in dense media

- Physical model suggests increased density favors multiple consecutive collisions

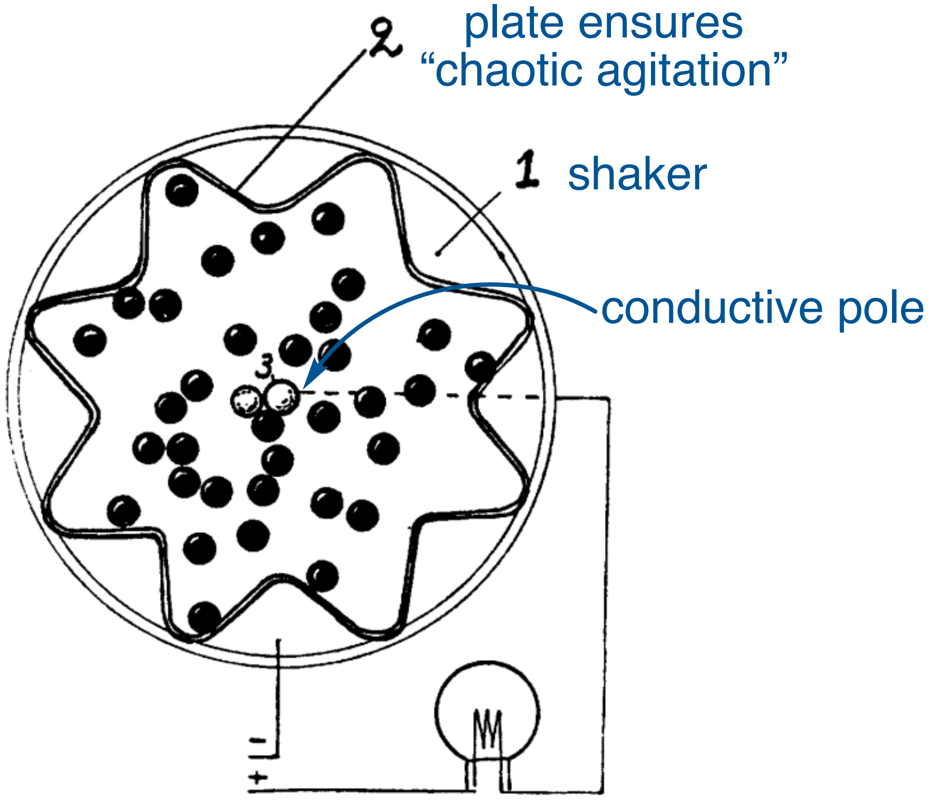
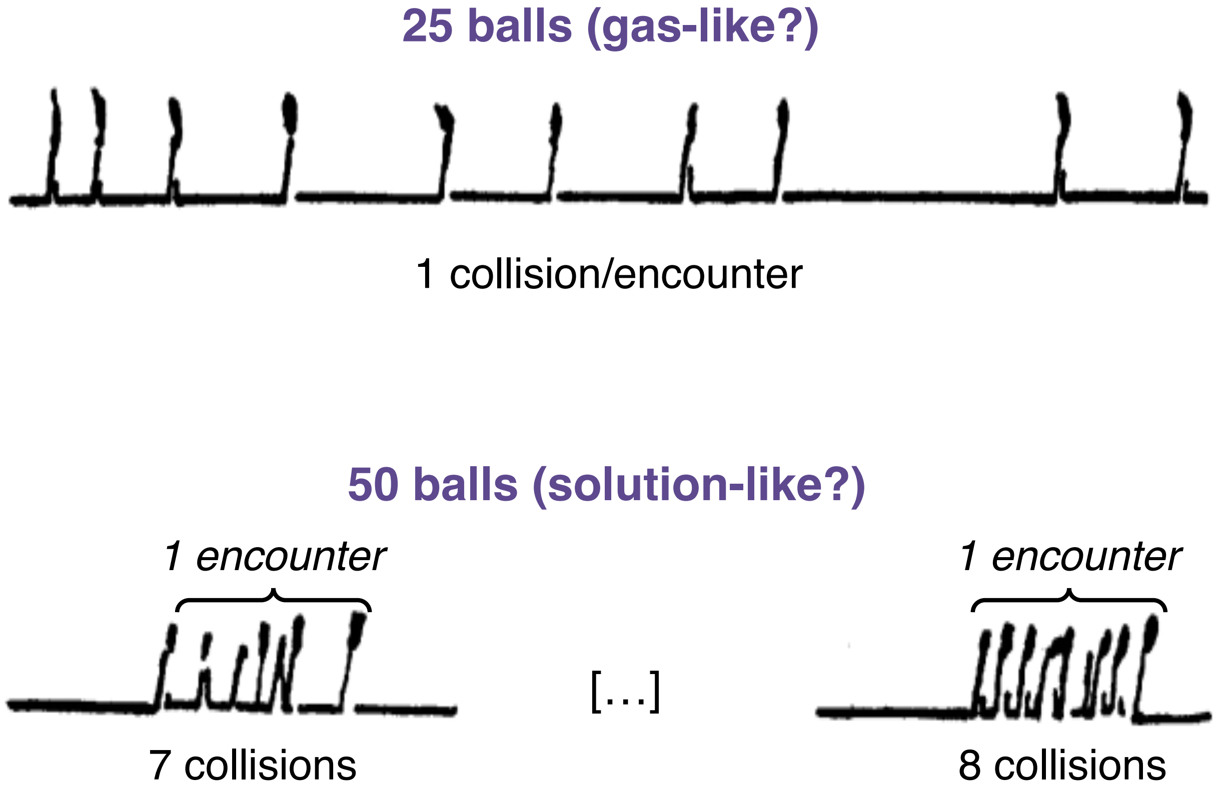


Fig. 2.

○ conductive ball (1)

● insulating ball (*N*)



when the conductive ball contacts the conductive pole, a signal is measured

total number of collisions is independent of the number of balls

Rabinowitsch, E.; Wood, W. C. *Trans. Faraday Soc.* **1936**, *32*, 1381–1387.

Early "experimental" support for cage effects in dense media

- Physical model suggests increased density favors multiple consecutive collisions

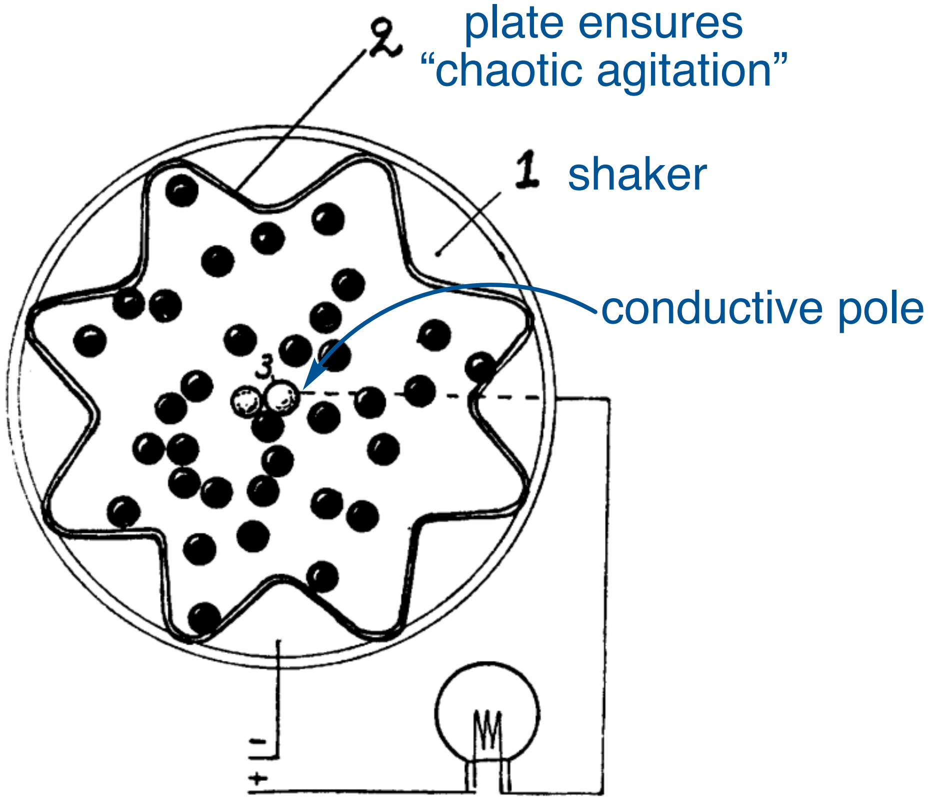
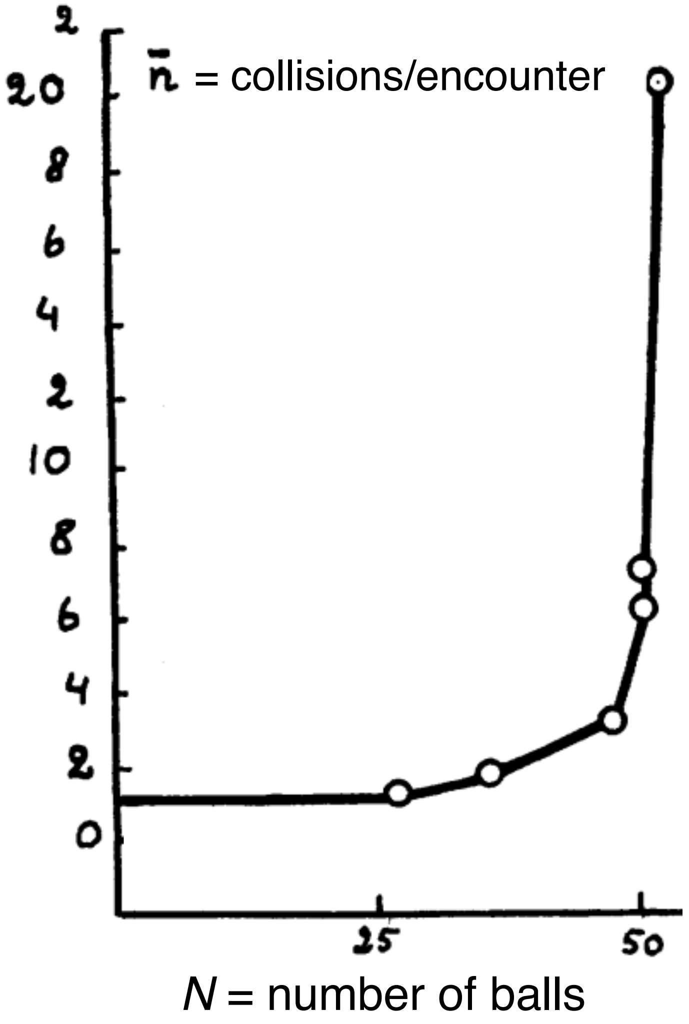


Fig. 2.

● conductive ball (1)

● insulating ball (N)



when the conductive ball contacts the conductive pole, a signal is measured

↑ N ➡

number of collisions remains constant

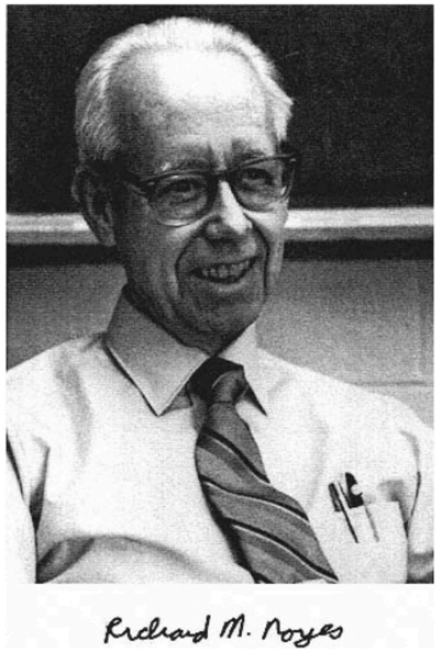
collisions per encounter increases

number of encounters decreases

Rabinowitsch, E.; Wood, W. C. *Trans. Faraday Soc.* **1936**, *32*, 1381–1387.

Theoretical model of radical cage effects

- Noyes model predicts dependence on viscosity, initial separation, translational energy, mass, and radius


Richard M. Noyes

“Having absolutely no imagination,
I majored in chemistry”

“The only chemical reactions that
are well understood are those that
have not been investigated in detail”

$$\mathrm{A{-}B} \underset{k_r}{\overset{h\nu}{\rightleftarrows}} [\mathrm{A}\cdot\ \cdot\mathrm{B}] \underset{k_d}{\overset{k_d}{\rightleftarrows}} [\mathrm{A}\cdot \mid \cdot\mathrm{B}] \xrightarrow{k_d} \mathrm{A}\cdot + \mathrm{B}\cdot$$

primary cage *secondary cage* *free radicals*

α = probability of reaction per encounter

β = probability of reencounter

β' = probability that a pair of molecules separating from an encounter will eventually react

$$\beta' = \alpha\beta + \alpha(1-\alpha)\beta^2 + \alpha(1-\alpha)^2\beta^3 + \ldots = \alpha\beta/(1-\beta+\alpha\beta)$$

substitute for β; account for initial displacement

rearrange to solve for $F = k_d/k_r$

$$\boxed{F = \left(\frac{R_0 - 2b}{2b}\right) + \left(\frac{R_0}{2b}\right)\left[\left(\frac{A_T + \alpha A_E}{\alpha}\right)\left(\frac{1}{\eta}\right) + \left(\frac{A_T \cdot A_E}{\alpha}\right)\left(\frac{1}{\eta}\right)^2\right]}$$

R_0 = initial separation

b = diffusion radius

η = viscosity

$A_E = \dfrac{[m(h\nu - E)]^{1/2}}{6\pi b^2}$ = translation energy of the separating fragments

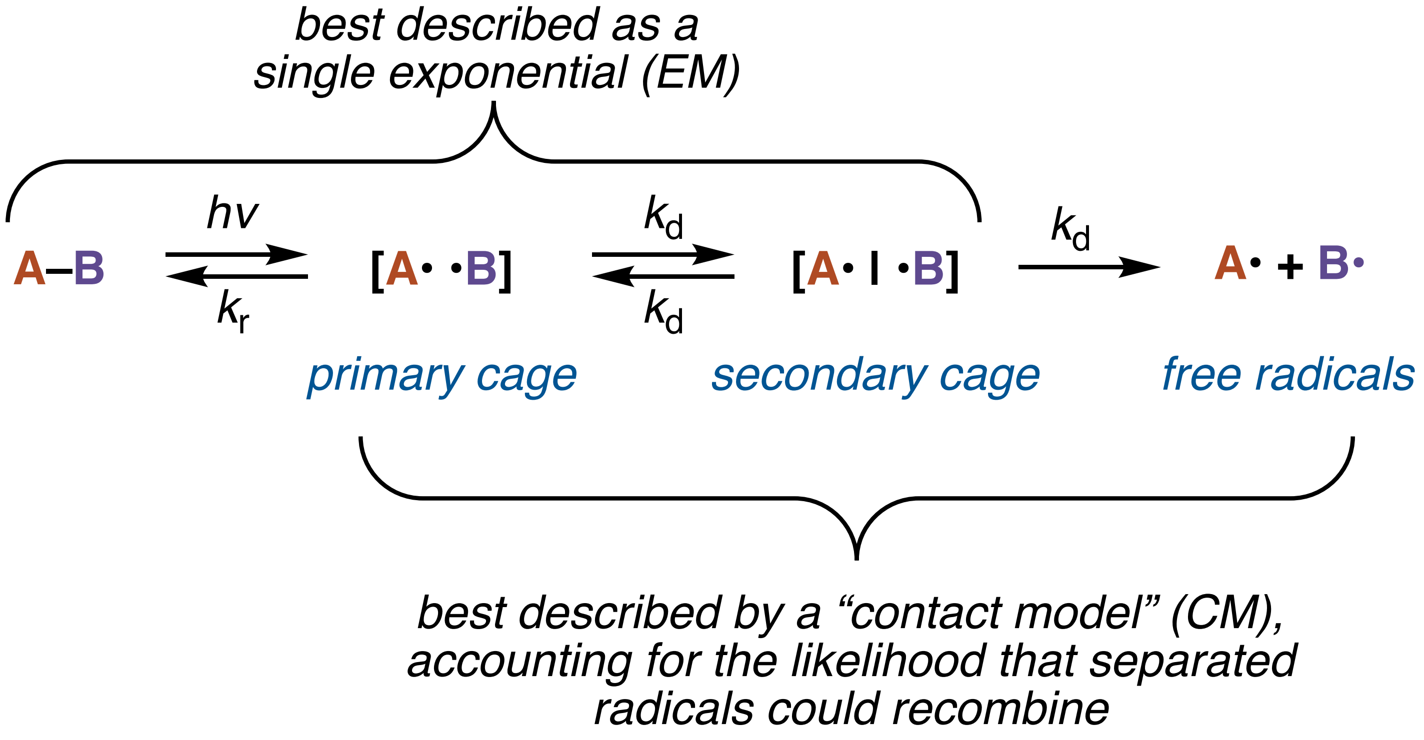
$A_T = \dfrac{[(3/2)mk_B T]^{1/2}}{6\pi b^2}$ = kinetic energy term

Noyes, R. M. *J. Am. Chem. Soc.* **1955**, *77*, 2042–2045.

Koenig, T.; Fischer, H. “Cage” Effects. In *Free Radicals*; Kochi, J., Ed.; Wiley: New York, 1973; Vol. 1; pp 164–170.

Theoretical model of radical cage effects

- More accurate models for cage reactions remain an active field of research



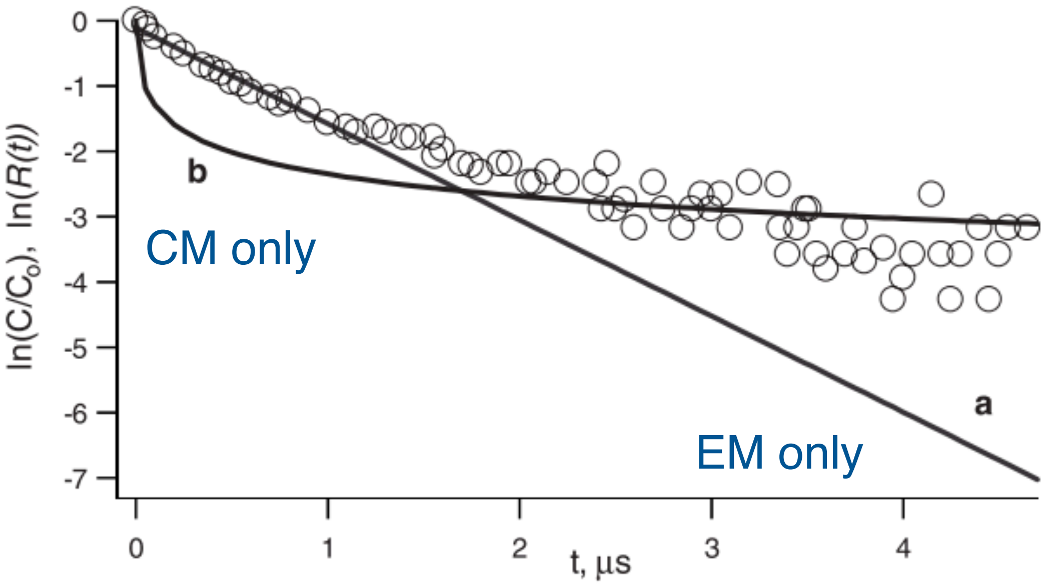
best described as a single exponential (EM)

$$A{-}B \underset{k_r}{\overset{h\nu}{\rightleftarrows}} [A\cdot\ \cdot B] \underset{k_d}{\overset{k_d}{\rightleftarrows}} [A\cdot \mid \cdot B] \xrightarrow{k_d} A\cdot + B\cdot$$

primary cage *secondary cage* *free radicals*

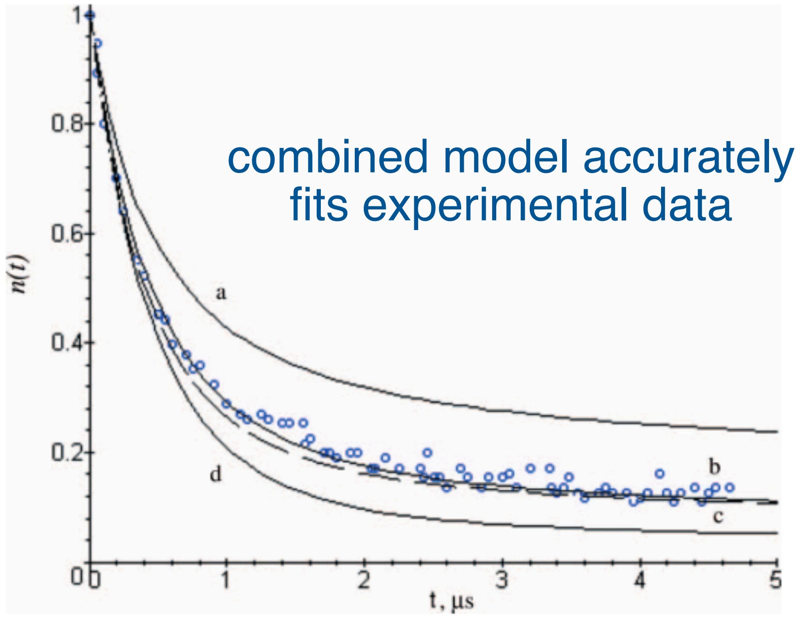
best described by a “contact model” (CM), accounting for the likelihood that separated radicals could recombine

generalized model = EM + CM



CM only

EM only



combined model accurately fits experimental data

Khudyakov, I.; Zharikov, A. A.; Burshtein, A. I. *J. Chem. Phys.* **2010**, *132*, 04104.

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Quantum yield of halide photodissociation

- Gas-phase data shows near perfect photodissociation efficiency

$$\mathrm{Br{-}Br} \xrightarrow[\phi \approx 1]{h\nu} 2\ \mathrm{Br}\cdot \qquad \mathrm{I{-}I} \xrightarrow[\phi \approx 1]{h\nu} 2\ \mathrm{I}\cdot$$

quantum yield ≈ 1
(gas phase)

- Solution data shows much lower quantum yield

$$\mathrm{Br{-}Br} \underset{k_r}{\overset{h\nu}{\rightleftharpoons}} [\mathrm{Br}\cdot\ \cdot\mathrm{Br}] \xrightarrow{k_d} 2\ \mathrm{Br}\cdot$$

solvent	***ϕ***
CCl_4	0.22

$$\mathrm{I{-}I} \underset{k_r}{\overset{h\nu}{\rightleftharpoons}} [\mathrm{I}\cdot\ \cdot\mathrm{I}] \xrightarrow{k_d} 2\ \mathrm{I}\cdot$$

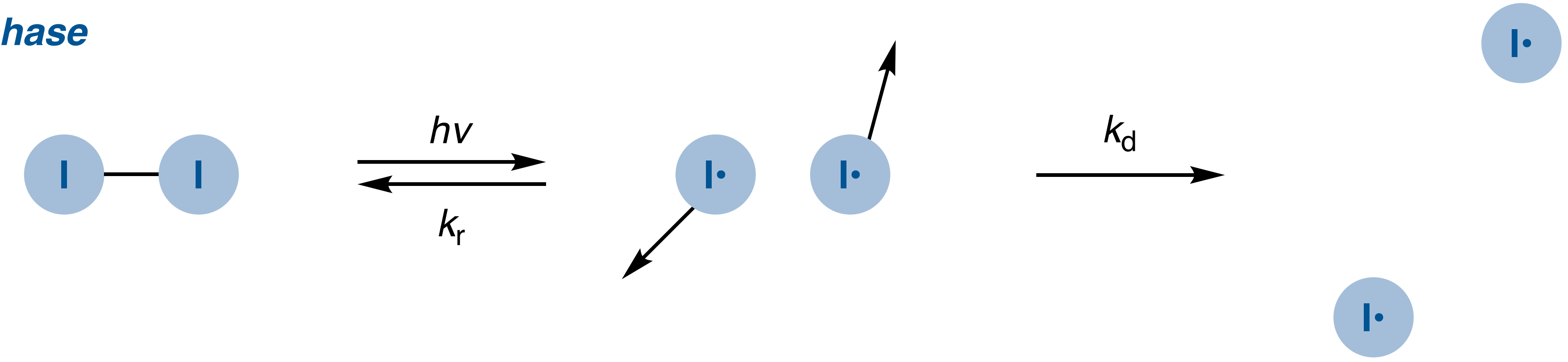
solvent	***ϕ***
hexanes	0.66
CCl_4	0.14
USP 335	0.04

Strong, R. L. *J. Am. Chem. Soc.* **1965**, *87*, 3563–3567.
Lampe, F. W.; Noyes, R. M. *J. Am. Chem. Soc.* **1954**, *76*, 2140–2144.
Noyes, R. M. *Z. Electrochem.* **1960**, *69*, 153–156

Effect of solvent on quantum yield supports cage effects

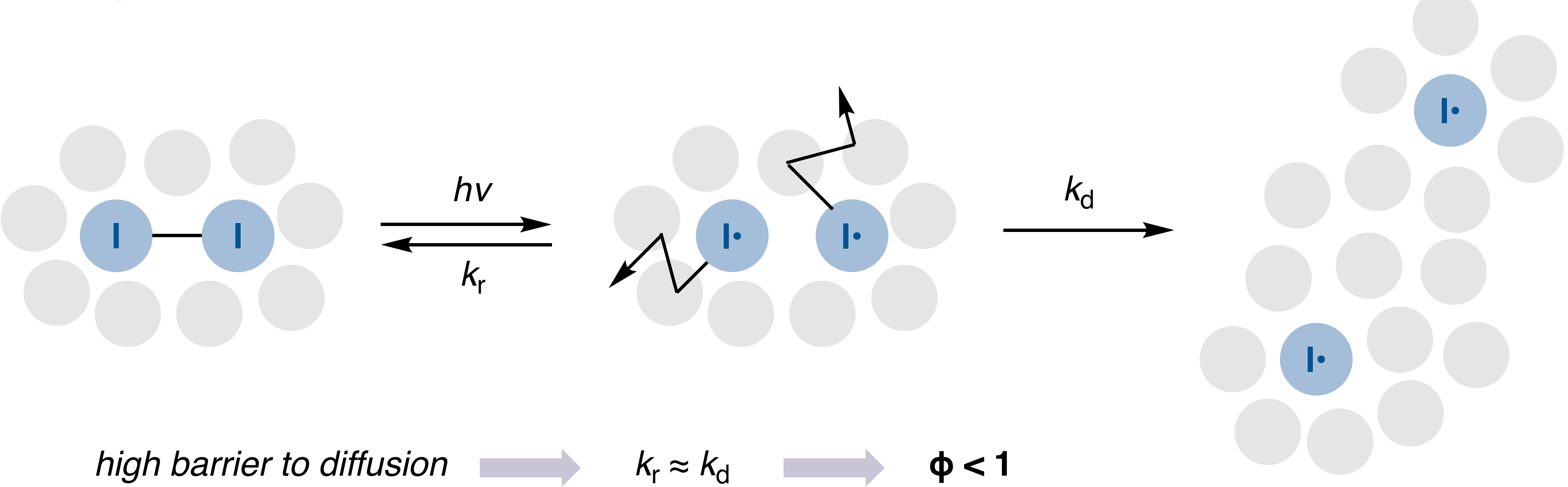
- Effect of solvent on quantum yield rationalized based on cage effect

gas phase



low barrier to diffusion → $k_d >> k_r$ → $\phi \approx 1$

solution phase



high barrier to diffusion → $k_r \approx k_d$ → $\phi < 1$

Quantum yield of halide photodissociation

- Iodine, azo photodissociation quantum yields show significant solvent viscosity effects

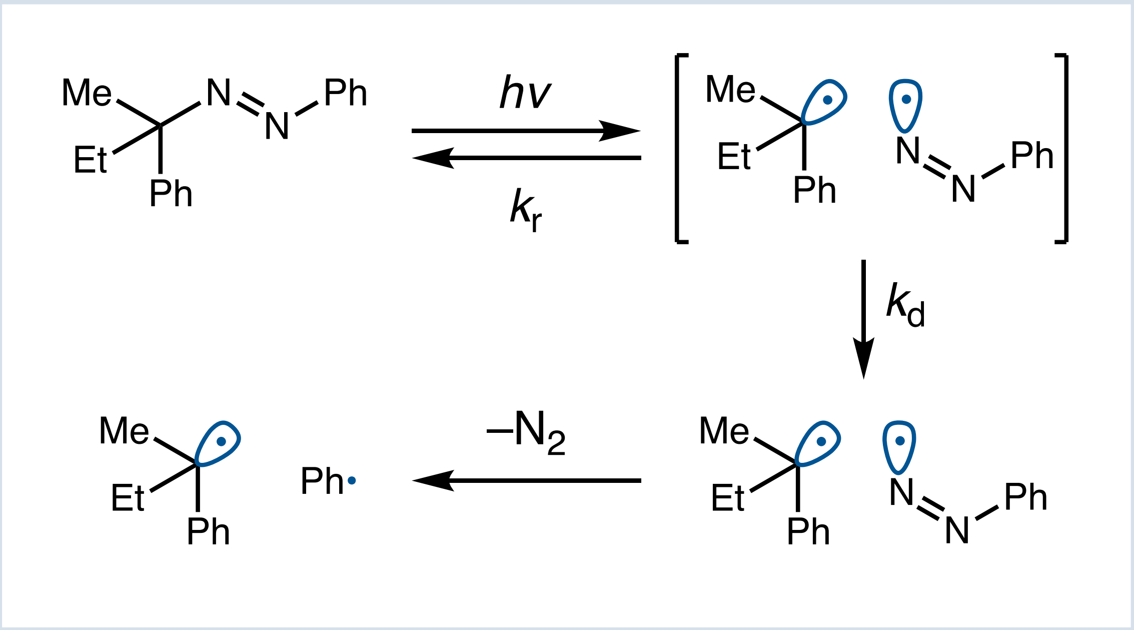
$$I{-}I \underset{k_r}{\overset{h\nu}{\rightleftharpoons}} [I\cdot\ \cdot I] \xrightarrow{k_d} 2\ I\cdot$$

solvent	***η (cP)***	***ϕ***
hexane	0.29	0.66
Bayol D	1.7	0.18
NF 65	54	0.086
NF 95	80	0.048
USP 180	180	0.038

viscosity ↓

quantum yield ↑

quantum yield decreases with increasing solvent viscosity



solvent	***ϕ***
octane	0.044
decane	0.039
dodecane	0.035
hexadecane	0.029

viscosity ↓

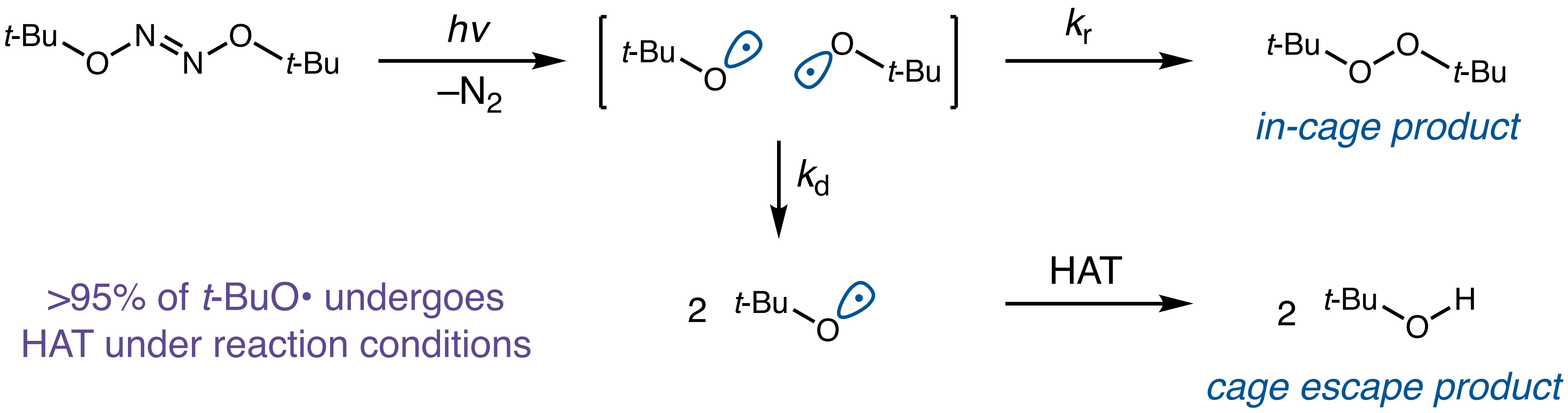
quantum yield ↑

Noyes, R. M. *Z. Electrochem.* **1960**, *69*, 153–156

Porter, N. A.; Landis, M. E.; Marnett, L. J. *J. Am. Chem. Soc.* **1971**, *93*, 795–796.

Effect of viscosity on product ratios

- Product ratios in hyponitrite decomposition support presence of cage effects



in-cage product

cage escape product

>95% of *t*-BuO• undergoes HAT under reaction conditions

% Nujol in octadecane	***η* (cP)**	***F*$_{cP}$**
20%	0.6	0.16
40%	1.1	0.21
60%	2.8	0.30
70%	4.7	0.36
80%	8.7	0.46
90%	22	0.56

viscosity ↓

t-BuOH/(t-BuO)$_2$ ↑

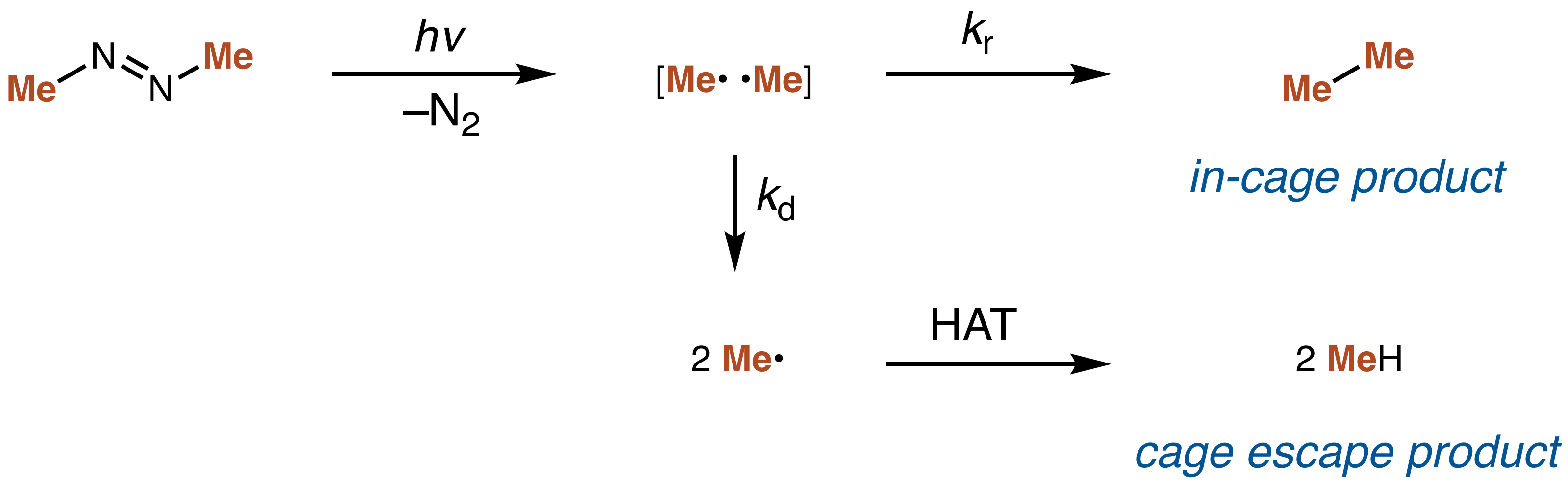
$$F_{cP} = \frac{(t\text{-BuO})_2}{(t\text{-BuO})_2 + t\text{-BuOH}/2}$$

fraction of radicals that react in-cage

Porter, N. A.; Landis, M. E.; Marnett, L. J. *J. Am. Chem. Soc.* **1971**, *93*, 795–796.

Formation of ethane from azomethane

- Quantum yield of ethane formation dramatically increases in condensed phases



in-cage product

cage escape product

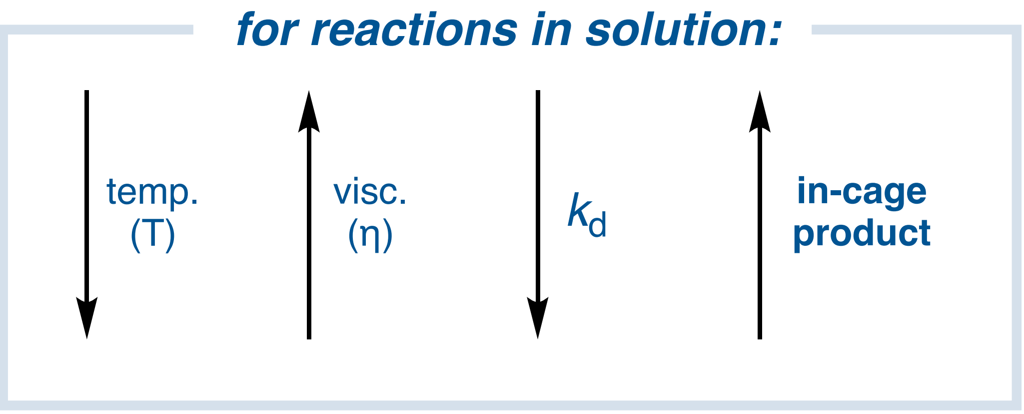
gas phase

$\Phi_{N2} \approx 1$ $\Phi_{EtH} \approx 0.04$

in cyclohexane

$\Phi_{N2} \approx 0.8$ $\Phi_{EtH} \approx 0.6$

for reactions in solution:



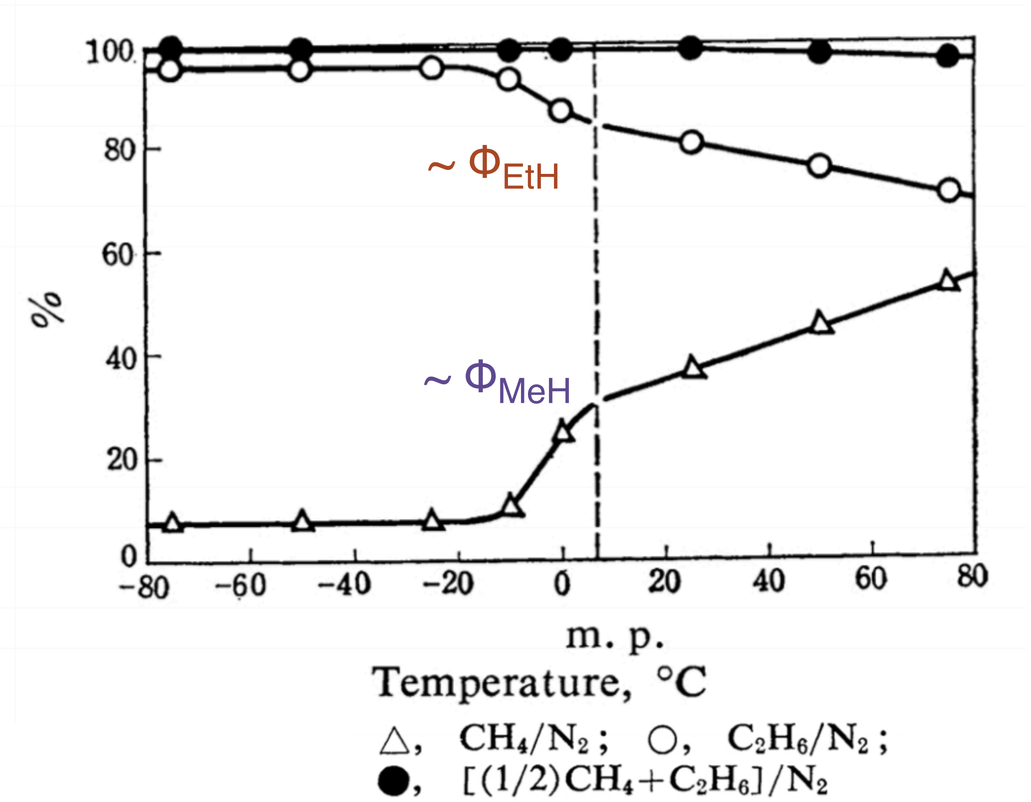
temp. (T)

visc. (η)

k_d

in-cage product

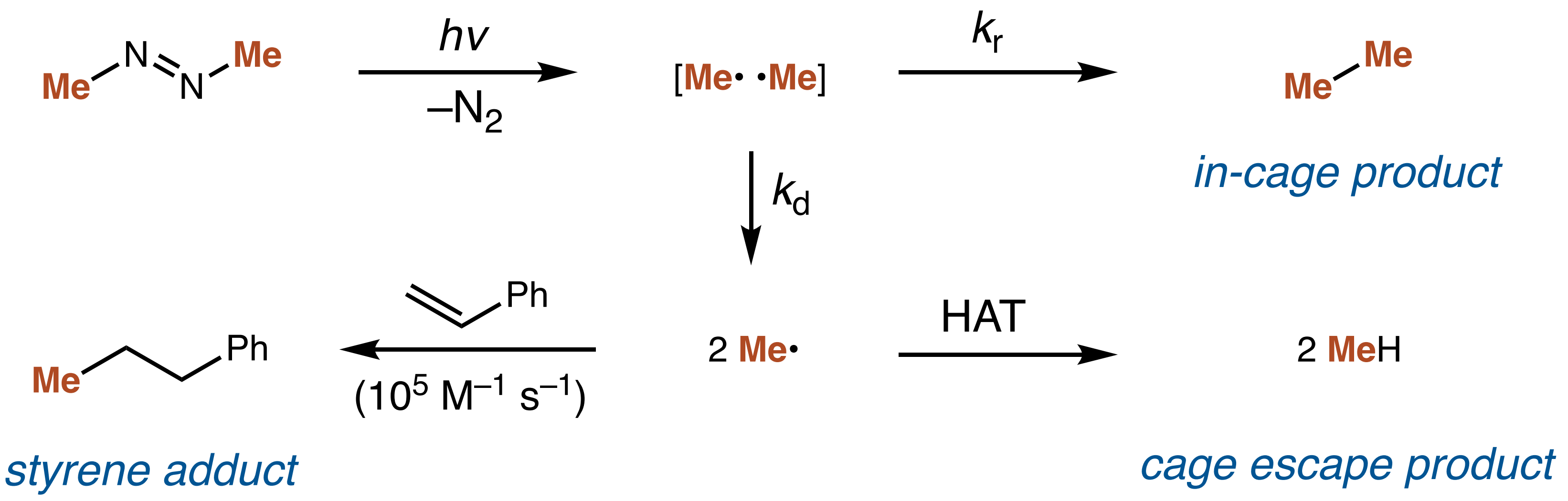
further increase in Φ_{EtH} observed in frozen solution



Lyon, R. K. *J. Am. Chem. Soc.* **1964**, *86*, 1907–1911.
Kodama, S. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 824–827.

Photolysis of azomethane in the presence of styrene

- Presence of potential quencher does not affect the rate of formation of ethane in solution

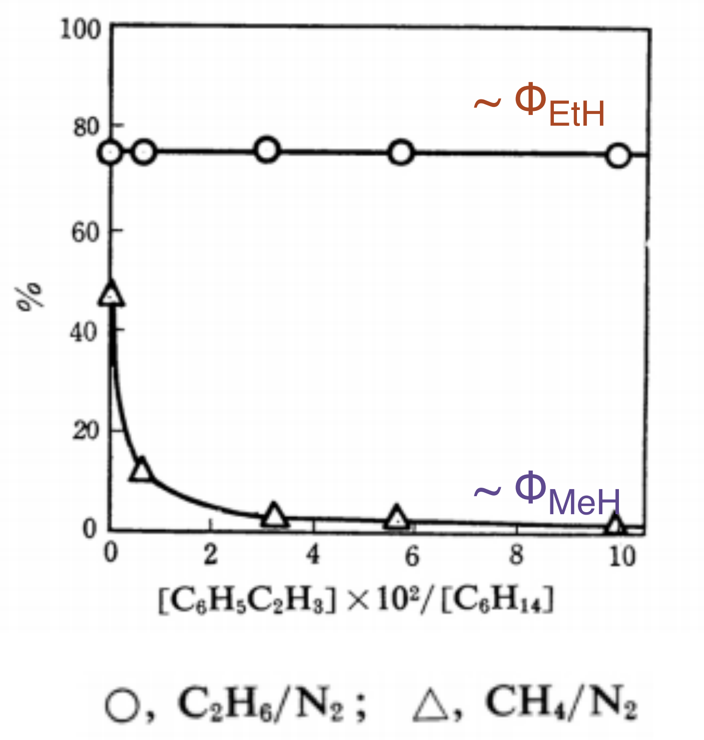


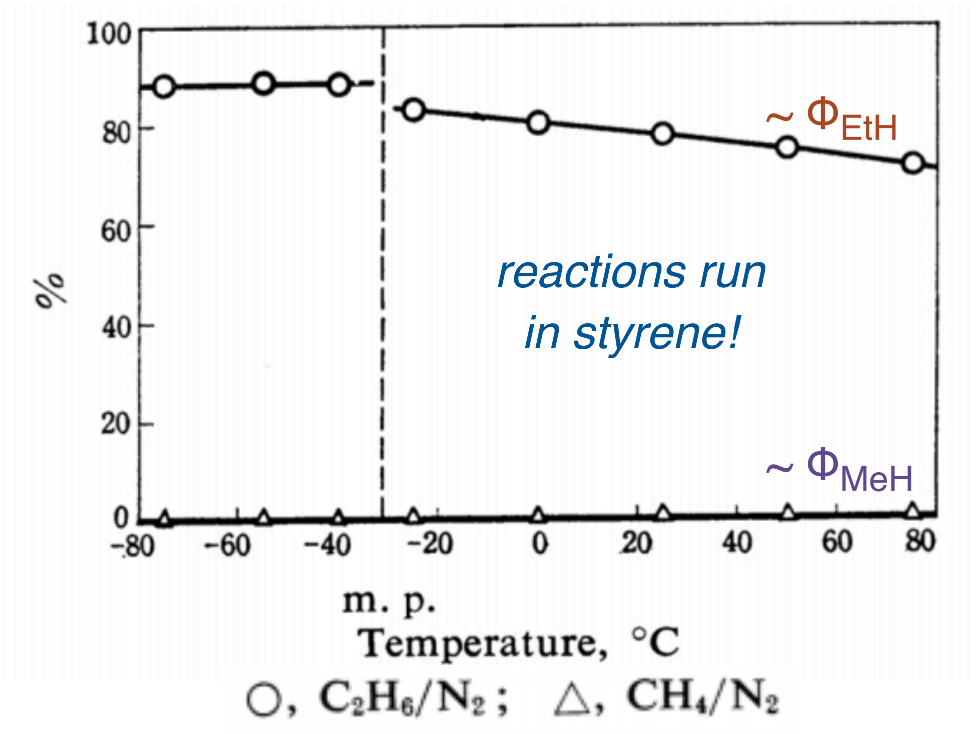
in-cage product

styrene adduct

cage escape product

results suggest all ethane is formed in solvent cage



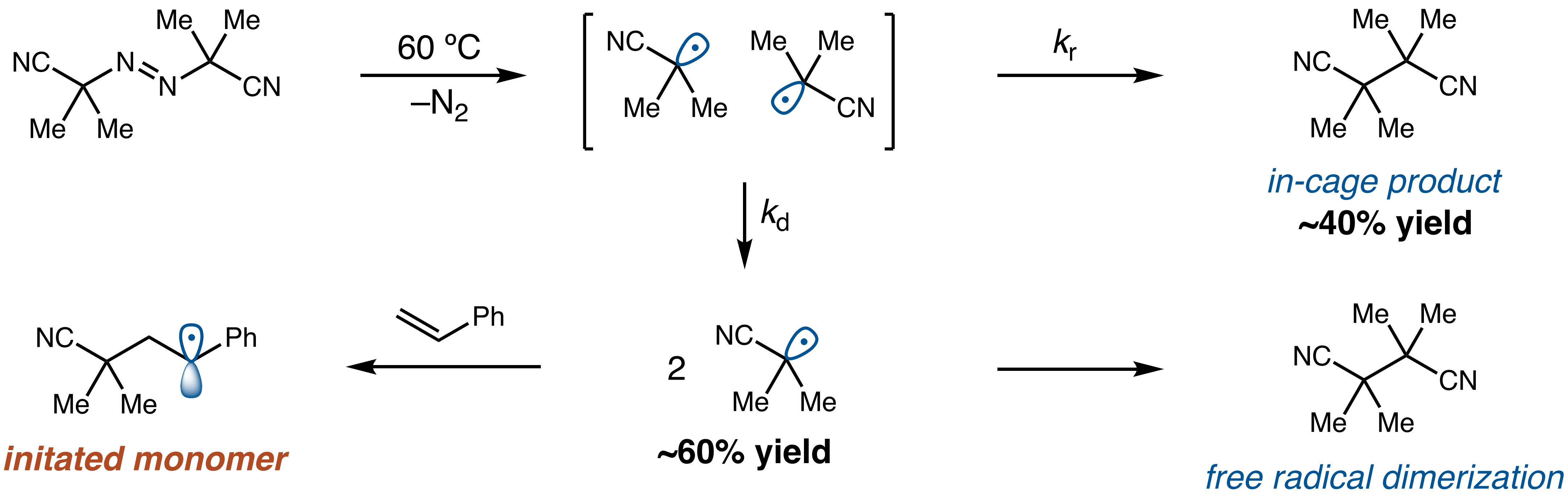


reactions run in styrene!

Kodama, S. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 652–657.
Kodama, S. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 824–827.

Cage effects in polymerization

- Under thermal conditions, a significant proportion of consumed AIBN does not initiate polymerization



in-cage product
~40% yield

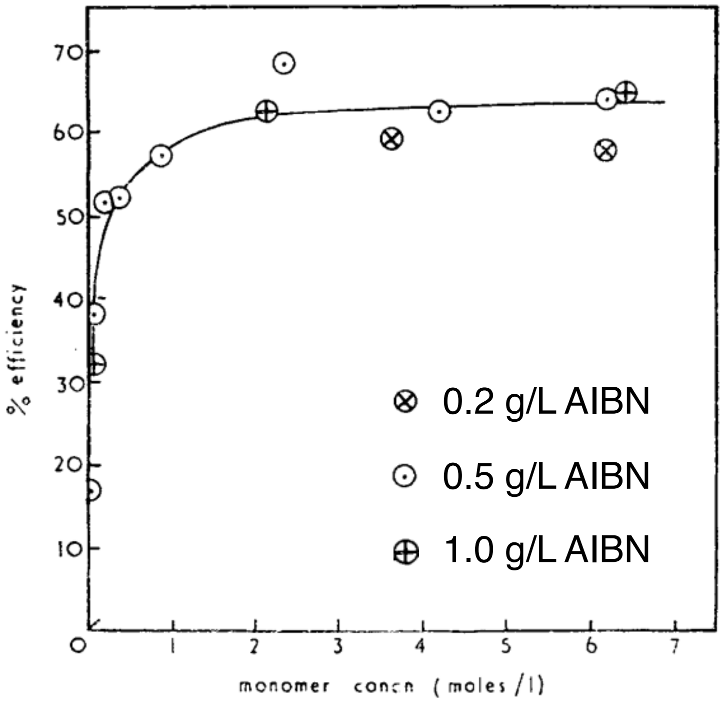
initated monomer

~60% yield

free radical dimerization

concentration dependent
at low [styrene]

free radical dimerization competitive with initiation



⊗ 0.2 g/L AIBN
⊙ 0.5 g/L AIBN
⊕ 1.0 g/L AIBN

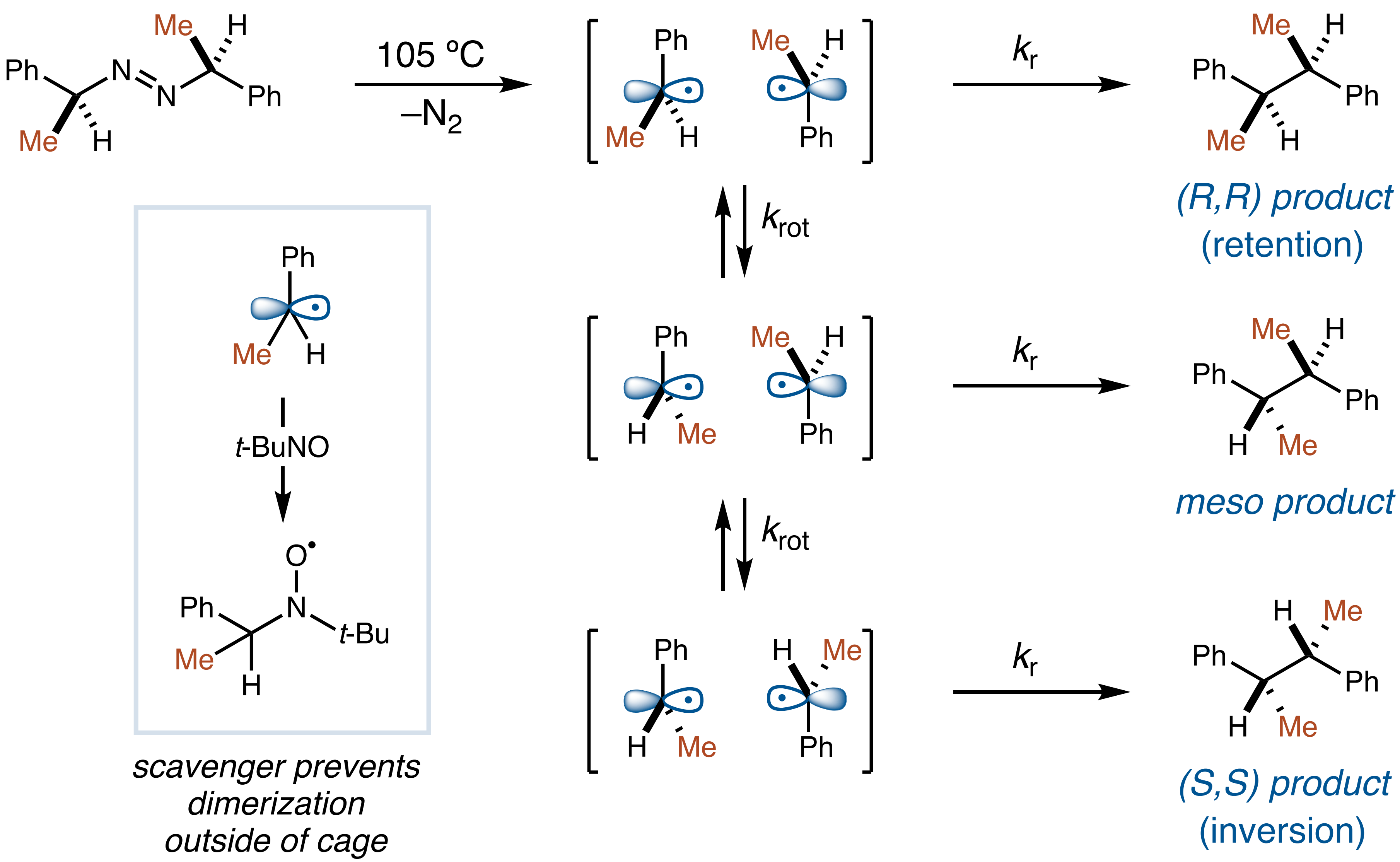
concentration independent
at high [styrene]

~40% of dimerization occurs in solvent cage

Bevington, J. C. *Trans. Faraday. Soc.* **1955**, *51*, 1392–1397.

Stereospecificity in in-cage recombination

- Stereorentention in radical-radical recombination product supports in-cage reaction



scavenger prevents dimerization outside of cage

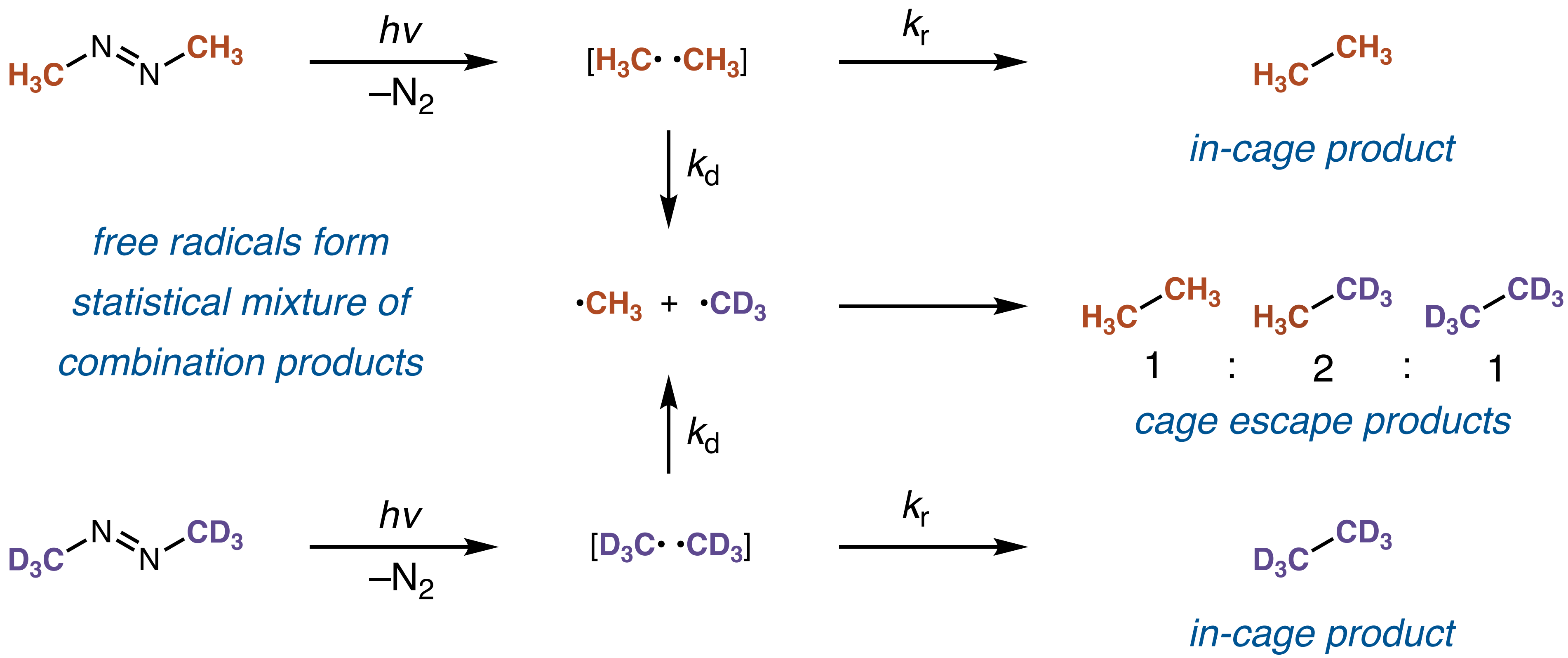
	without *t*BuNO	with *t*BuNO
(R,R) product (retention)	27%	31%
meso product	50%	48%
(S,S) product (inversion)	23%	21%
	(88% yield)	(28% yield)

recombination in cage is competitive with molecular rotation

Greene, F. D.; Berwick, M. A.; Stowell, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 867–874.

Isotopic labeling in azomethane photolysis

- Statistical mixture of products observed in gas phase, exclusively homoproducts observed in solution



in-cage product

free radicals form statistical mixture of combination products

cage escape products

in-cage product

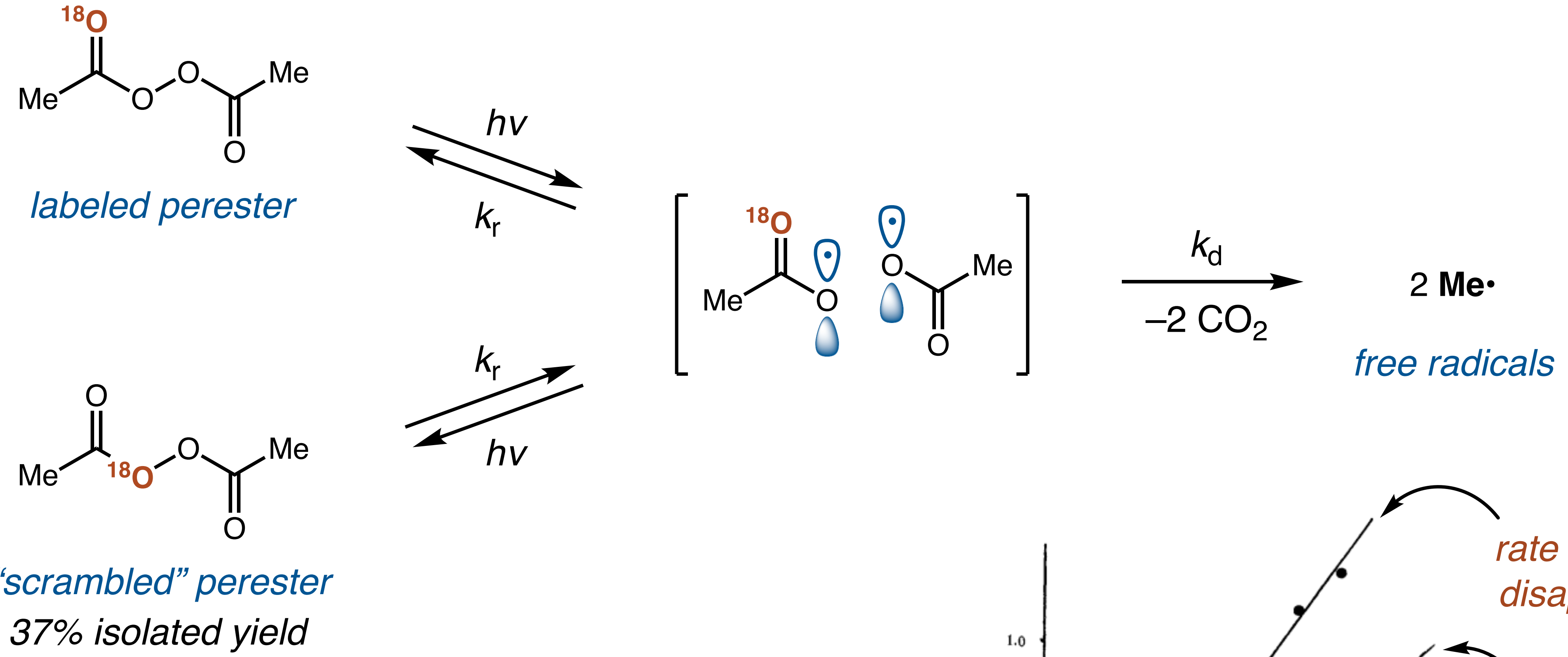
	CH_3CH_3	CH_3CD_3	CD_3CD_3
gas phase	25	50	25
isooctane	~50	<2	~50

recombination outcompetes cage escape in solution

Rebbert, R. E.; Ausloos, P. *J. Phys. Chem.* **1962**, *66*, 2253–2258.
Lyon, R. K.; Levy, D. H. *J. Am. Chem. Soc.* **1961**, *83*, 4290.

Isotope labeling experiments

- Perester decompositon shows oxygen scrambling competitive with free radical generation

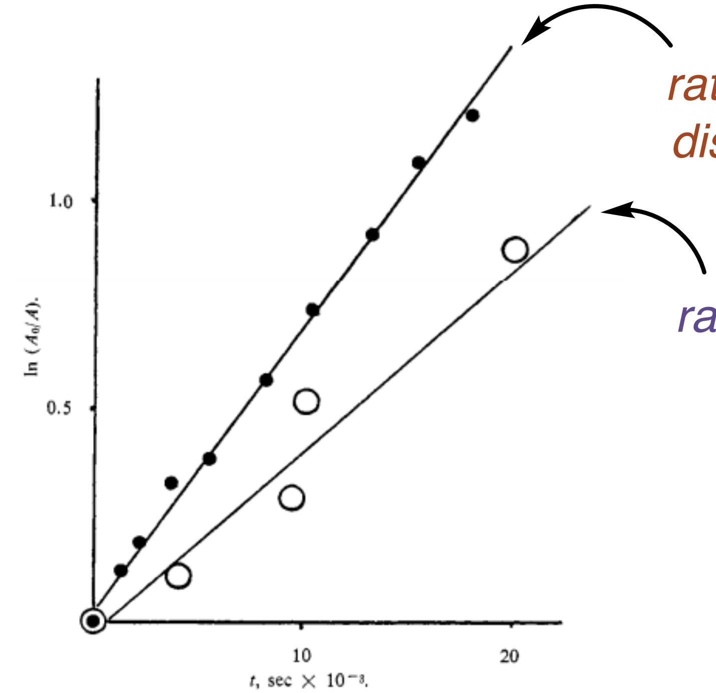


labeled perester

free radicals

“scrambled” perester

37% isolated yield



rate of perester disappearance

rate of perester scrambling

Figure 1. First-order rate plots for the disappearance of total acetyl peroxide (small circles, data obtained by infrared spectroscopy) and for scrambling of carbonyl label in recovered acetyl peroxide (large circles).

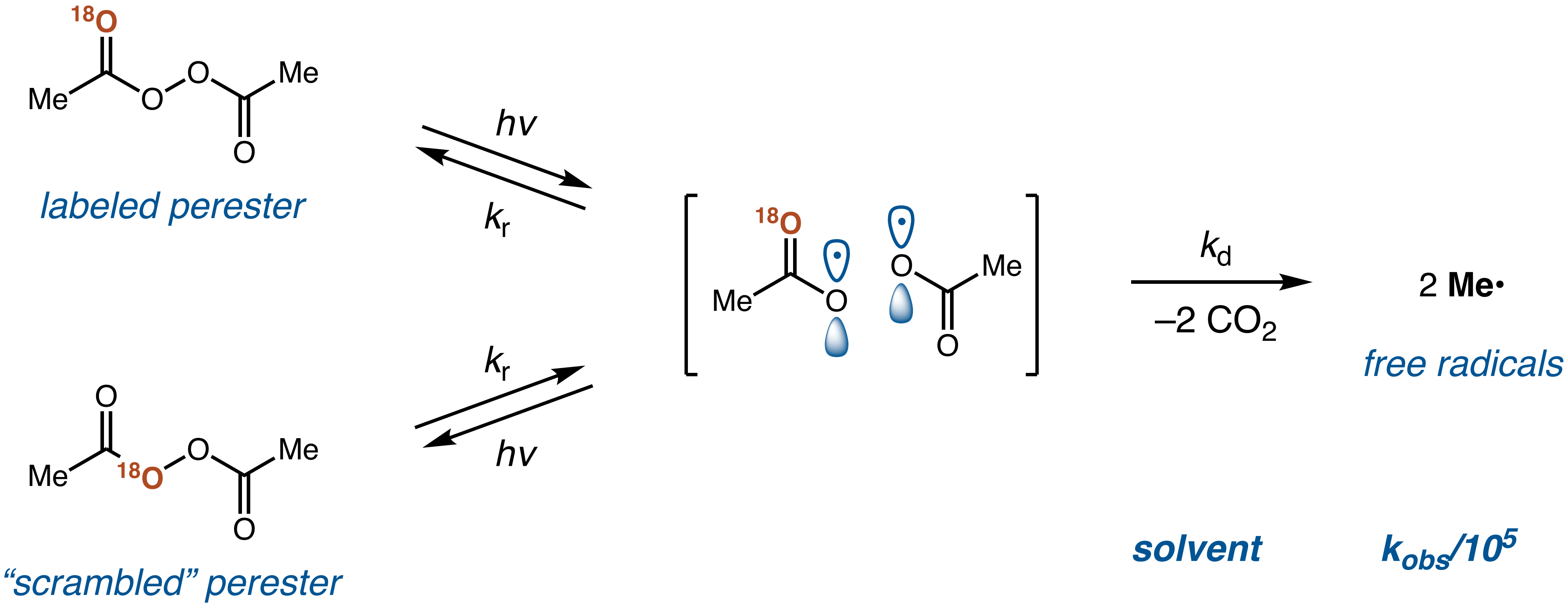
$\boldsymbol{k_r \approx k_d}$

in cage recombination is competetive with cage escape

Taylor, J. W.; Martin, J. C. *J. Am. Chem. Soc.* **1966**, *88*, 3650–3651.

Perester decomposition: viscosity effects

- The importance of cage effects to efficiency of methyl radical formation is supported by rate-viscosity relationship



solvent	***$k_{obs}/10^5$***
heptane	7.7
octane	7.3
decane	6.9
dodecane	6.3
tetradecane	6.0
hexadecane	5.4

$d(AcO)_2/dt$ is a function of solvent viscosity

supports in-cage recombination

Pryor, W. A.; Smith, K. *J. Am. Chem. Soc.* **1970**, *92*, 5403–5412.

Outline

- **Introduction to cage effects**
    - *General definition, theoretical predictions*

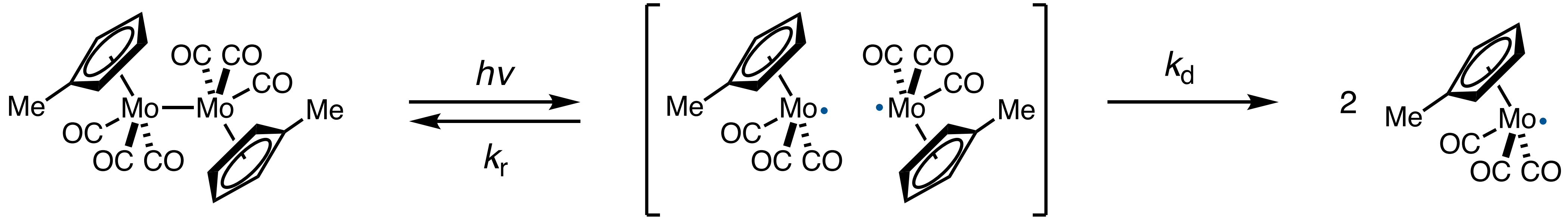
- **Experimental support for the existence of cage effects**
    - *Quantum yields, product ratios as a function of reaction medium*

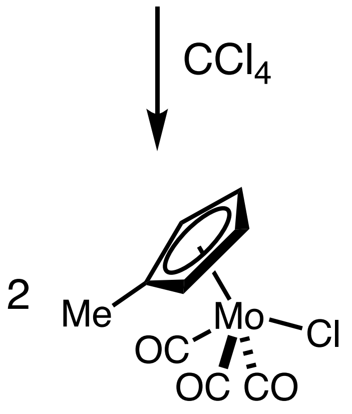
- **Parameters determining the magnitude of cage effects**
    - *Viscosity, reaction energetics, spin state, radical size, initial separation*

- **Recent case studies**
    - *Presence in biorelevant systems, transient absorption studies*

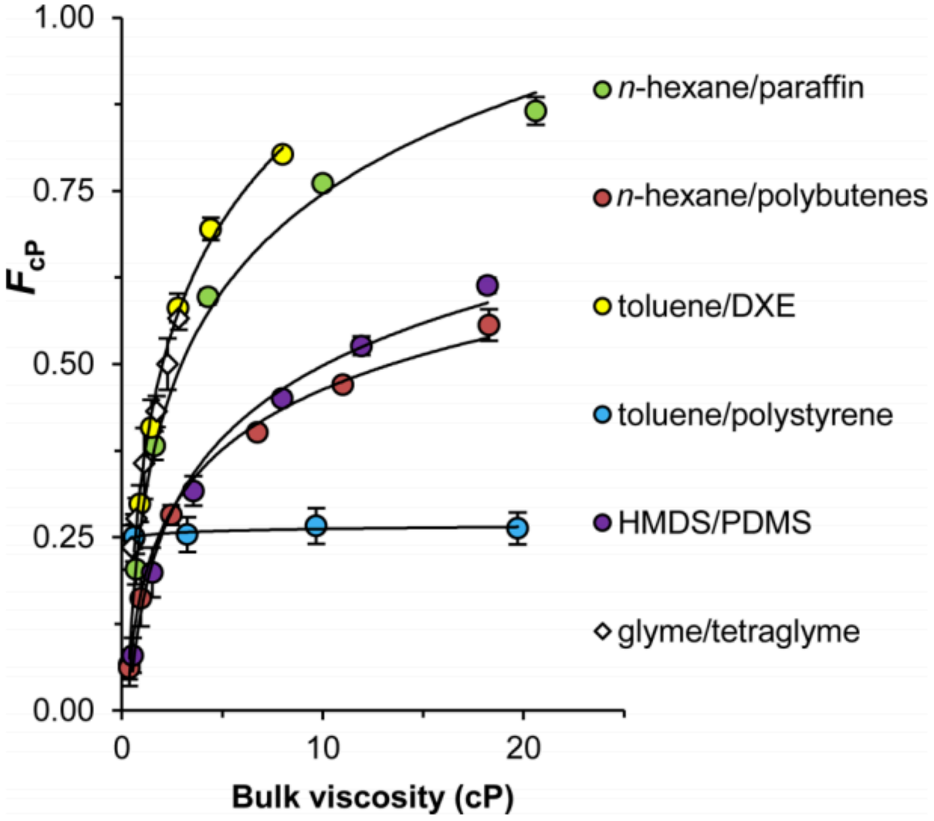
Effect of viscosity on cage efficiency

- Bulk viscosity provides predicts cage efficency for a single solvent system, but not between systems





all free radicals quenched



$$F_{cP} = \frac{k_r}{k_r + k_d}$$

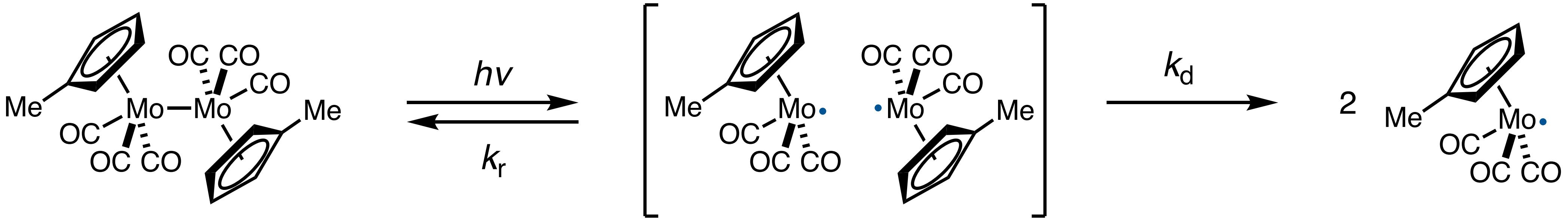
fraction of radicals that react in-cage

at a given bulk viscosity, different solvents give different cage efficiencies

Barry, J. T.; Berg, D. J.; Tyler, D. R. *J. Am. Chem. Soc.* **2016**, *138*, 9389–9392.
Barry, J. T.; Berg, D. J.; Tyler, D. R. *J. Am. Chem. Soc.* **2017**, *139*, 14399–14405.

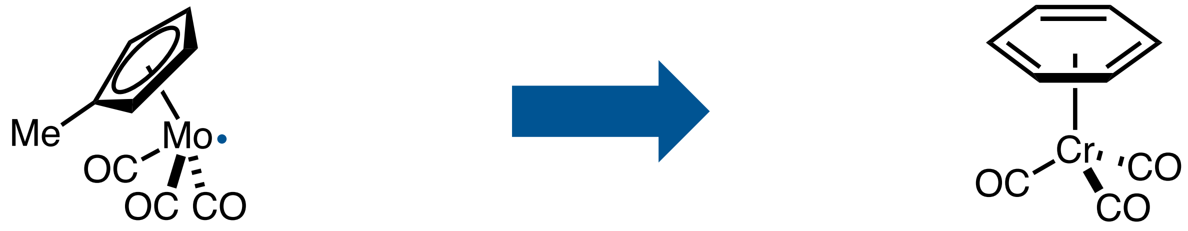
Microviscosity as a better predictor of cage effects

- Bulk viscosity does not necessarily predict rate of diffusion at a molecular scale



How can we measure the rate of diffusion of a transient radical?

diffusion measured via DOSY



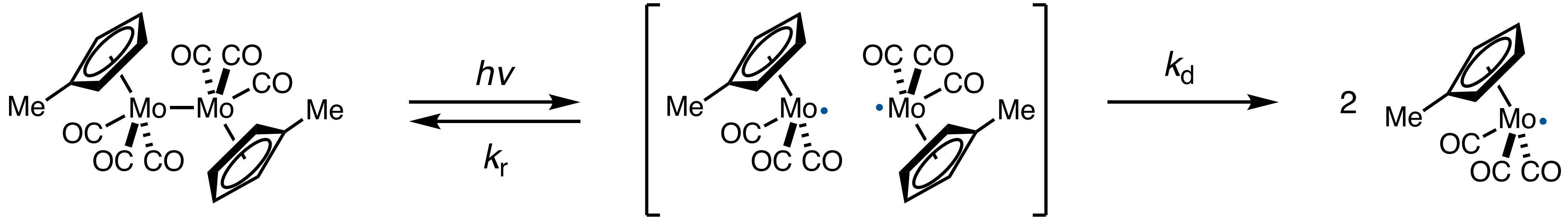
Δ mass = –40.9 Da
Δ vol. = –6.81 $Å^3$
Δ dipole = –1.37 D

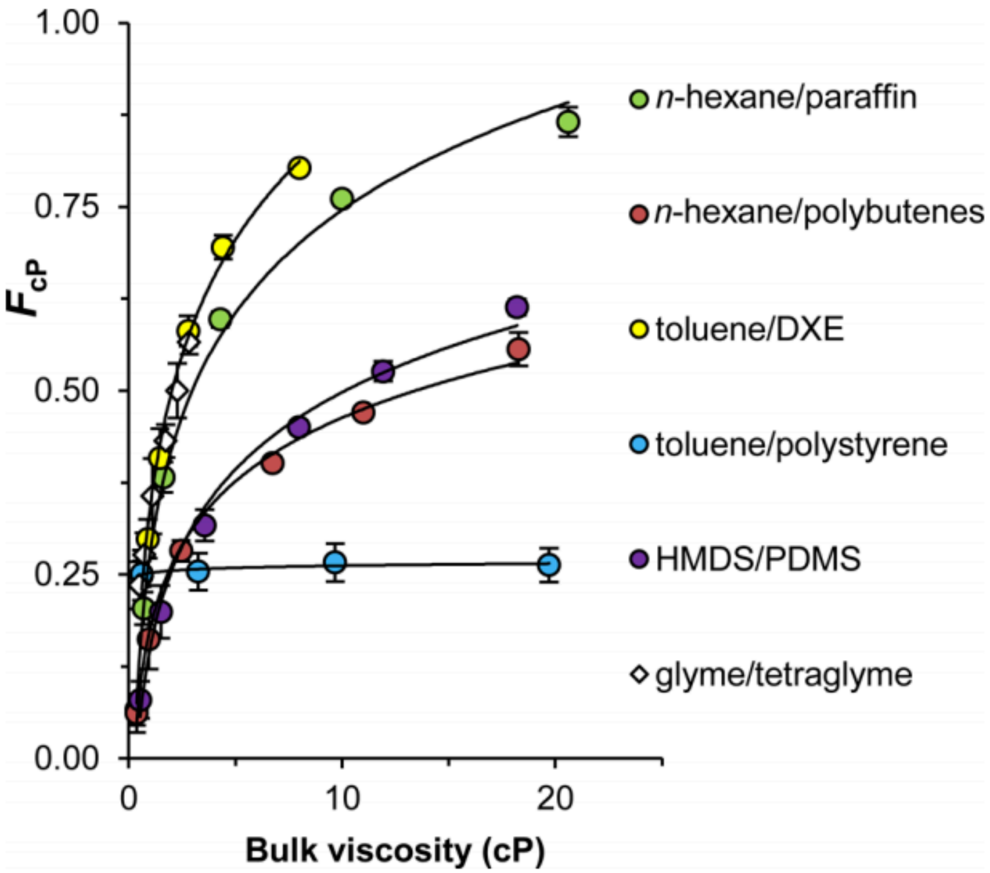
solvent	***bulk viscosity (cP)***	***microviscosity (s/m^2) × 10^9***
n-hexane/parrafin	0.36–20.61	0.29–6.28
toluene/polystyrene	0.61–30.22	0.60–0.83
methanol/tetraglyme	0.66–2.86	0.59–2.22

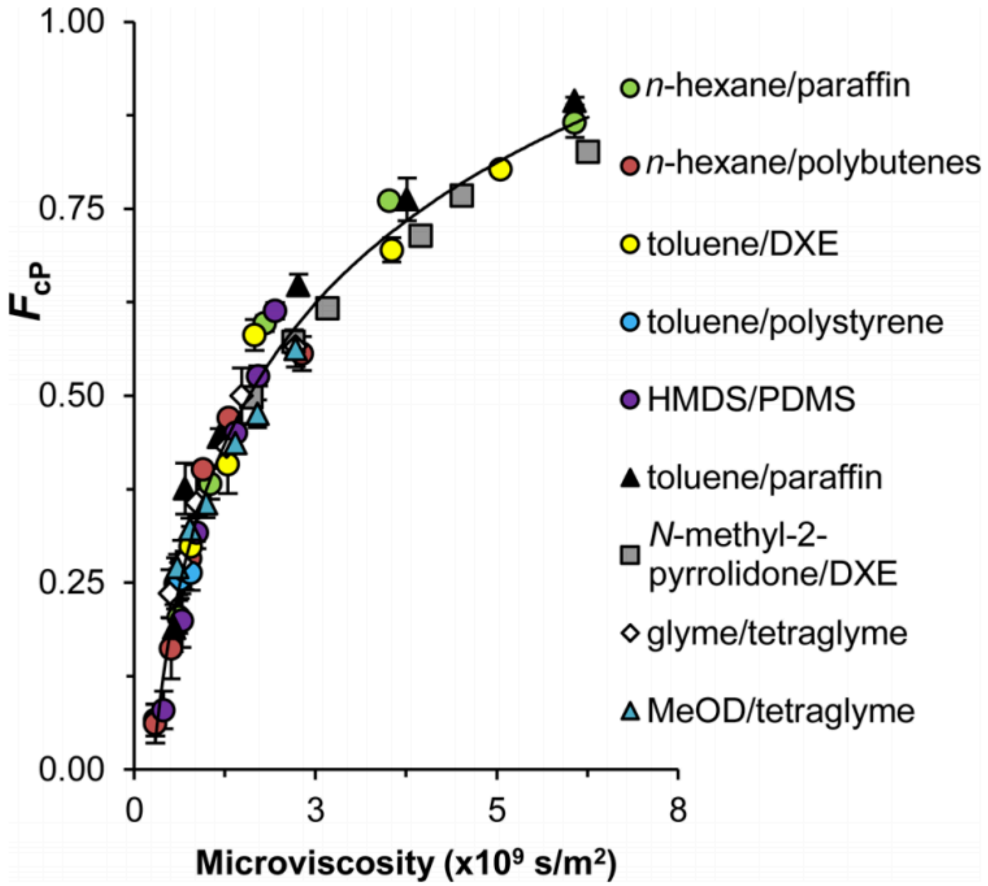
Barry, J. T.; Berg, D. J.; Tyler, D. R. *J. Am. Chem. Soc.* **2016**, *138*, 9389–9392.
Barry, J. T.; Berg, D. J.; Tyler, D. R. *J. Am. Chem. Soc.* **2017**, *139*, 14399–14405.

Microviscosity as a better predictor of cage effects

- Microviscosity enables successful prediction across solvent systems



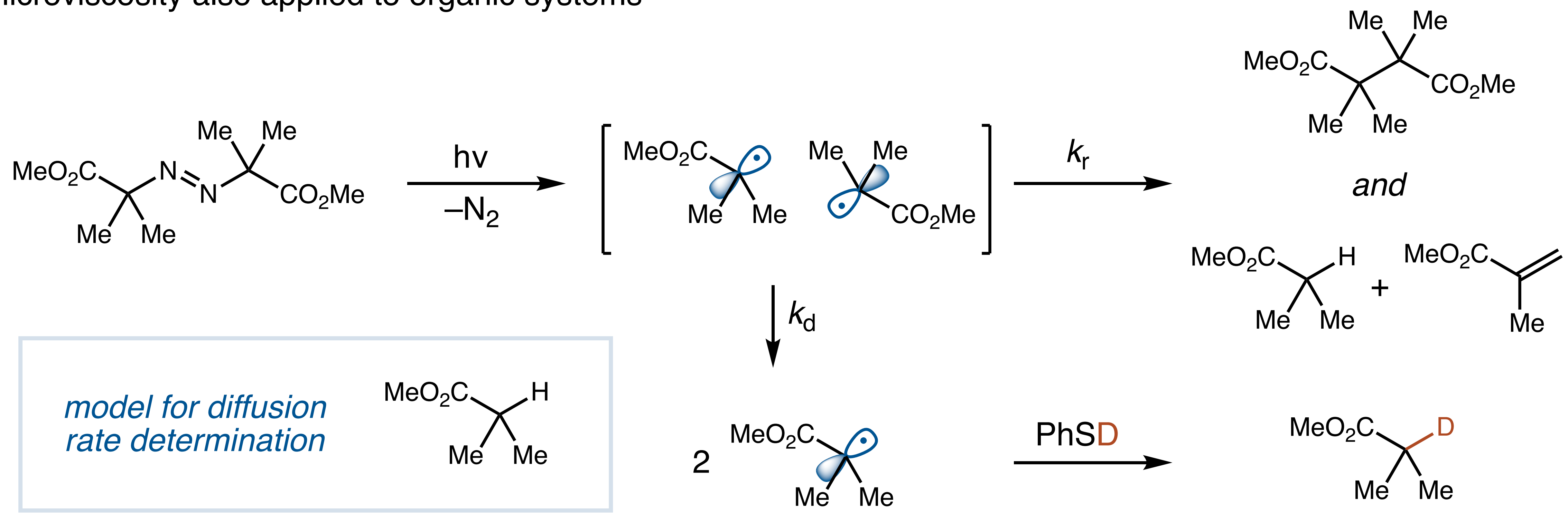




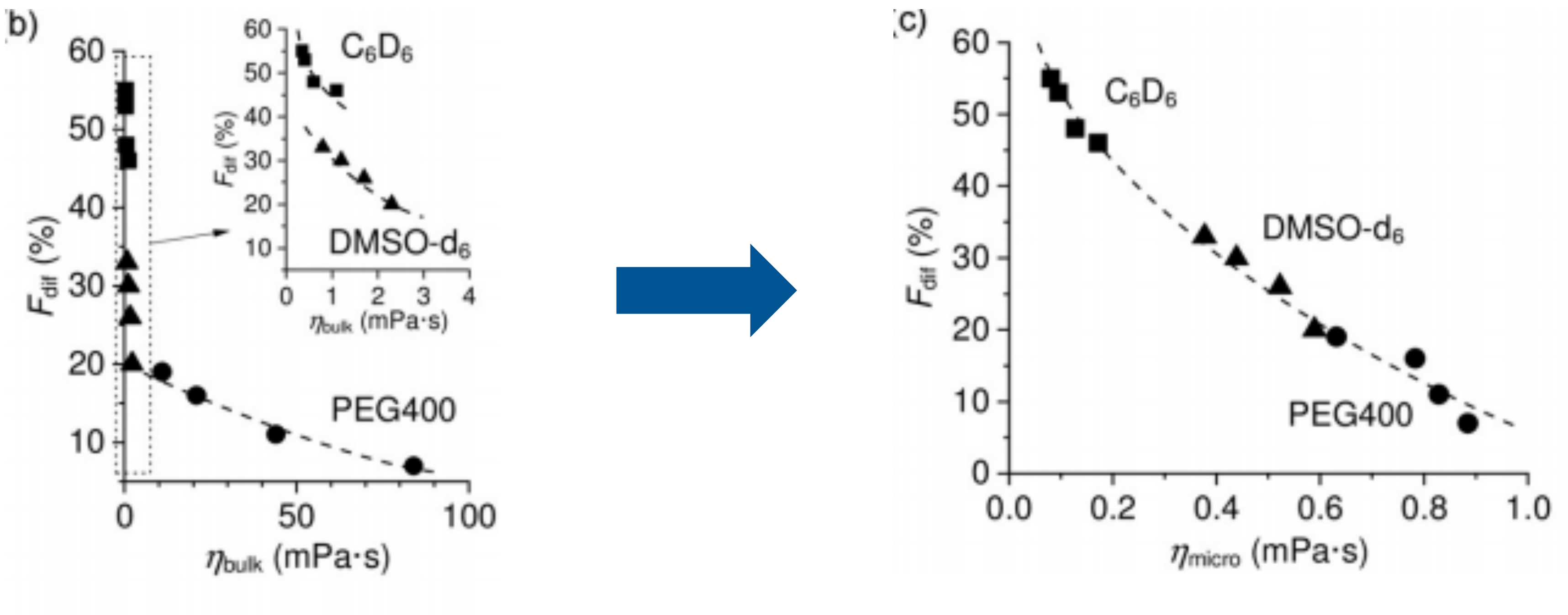
Barry, J. T.; Berg, D. J.; Tyler, D. R. *J. Am. Chem. Soc.* **2016**, *138*, 9389–9392.
Barry, J. T.; Berg, D. J.; Tyler, D. R. *J. Am. Chem. Soc.* **2017**, *139*, 14399–14405.

Application of microviscosity to organic radicals

- Microviscosity also applied to organic systems



model for diffusion rate determination



Li, X.; Ogihara, T.; Abe, M.; Nakamura, Y.; Yamago, S. *Chem. Eur. J.* **2019**, *25*, 9846–9850.

Effect of irradiation wavelength on cage efficiency

- Iodine, chlorine photodissociation show significant wave length effects

$$X{-}X \underset{k_r}{\overset{h\nu}{\rightleftarrows}} [X\cdot\ \cdot X] \xrightarrow{k_d} 2\,X\cdot$$

I_2 in hexane

λ (nm)	$h\nu - E_{I-I}$ (kcal/mol)	ϕ
405	35.0	0.83
436	30.0	0.66
546	16.6	0.46
579	13.9	0.44
643	8.9	0.40
735	3.3	0.31

Cl_2 in CCl_4

λ (nm)	$h\nu - E_{Cl-Cl}$ (kcal/mol)	ϕ
308	35	0.16
337	27	0.22

higher excess photonic energy

↓

higher excess kinetic energy of products

↓

more efficient cage escape

↓

higher quantum yield of radical generation

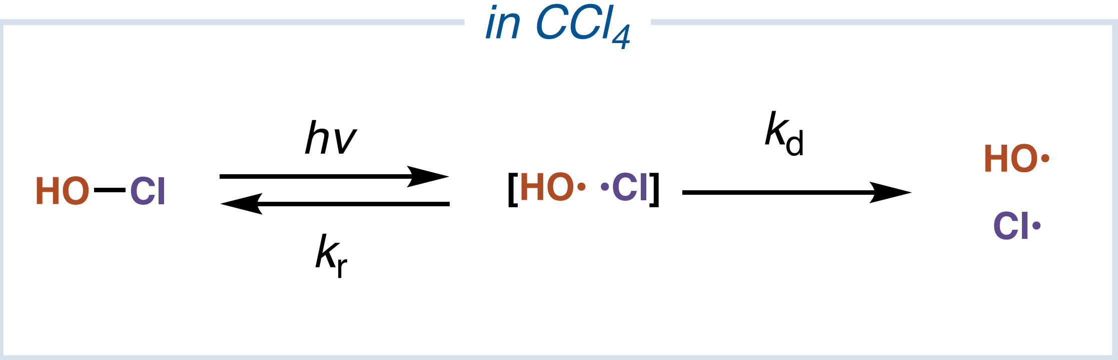
Meadows, L. F.; Noyes, R. M. *J. Am. Chem. Soc.* **1960**, *82*, 1872–1876

Clark, K. B.; Griller, D. *Chem. Phys. Lett.* **1990**, *168*, 477–481.

Are these effects present in polyatomic radicals?

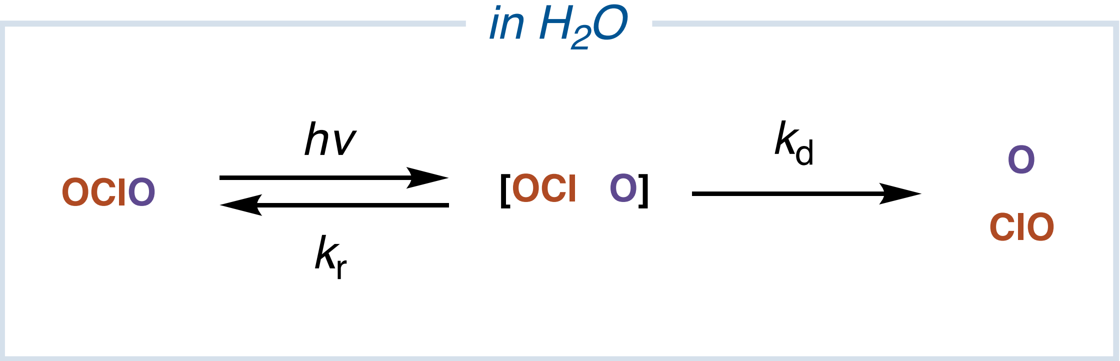
- Small polyatomics show similar effects of irradiation wavelength on cage escape

in CCl_4

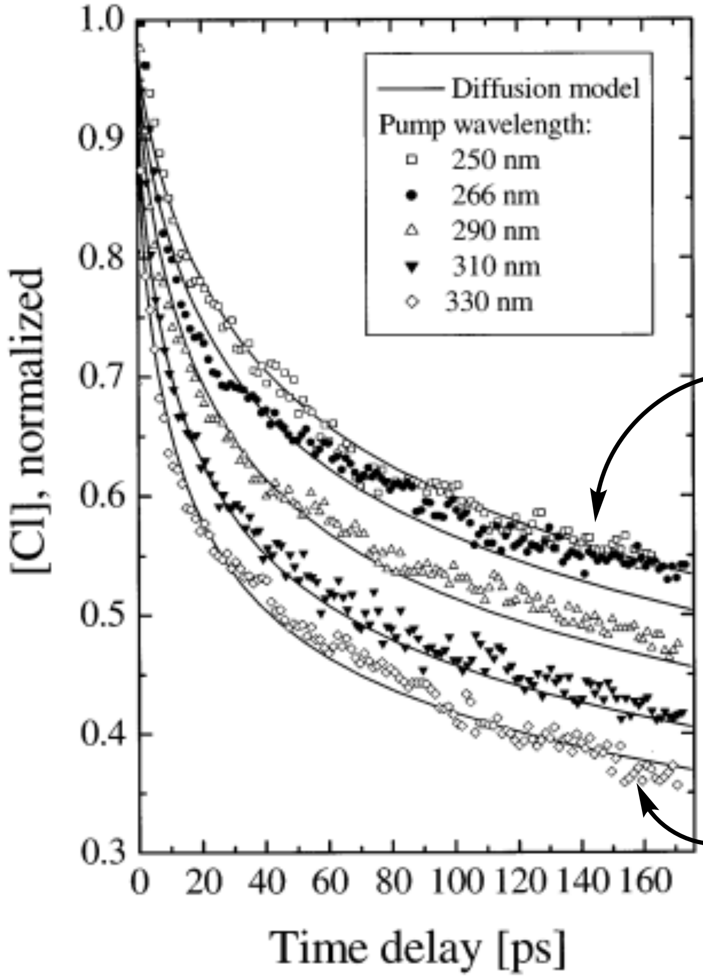


$$\mathrm{HO{-}Cl} \underset{k_r}{\overset{h\nu}{\rightleftharpoons}} [\mathrm{HO\cdot\ \cdot Cl}] \xrightarrow{k_d} \mathrm{HO\cdot}\ \ \mathrm{Cl\cdot}$$

in H_2O

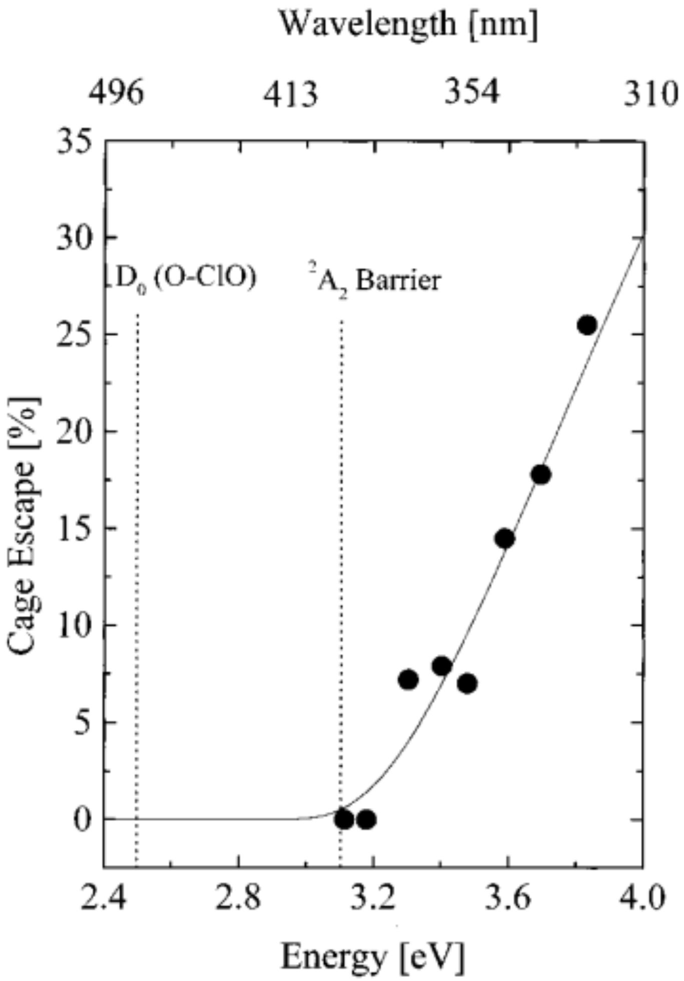


$$\mathrm{OClO} \underset{k_r}{\overset{h\nu}{\rightleftharpoons}} [\mathrm{OCl}\ \ \mathrm{O}] \xrightarrow{k_d} \mathrm{O}\ \ \mathrm{ClO}$$



highest energy
most cage escape
slowest recombination

lowest energy
least cage escape
fastest recombination



higher energy light

↓

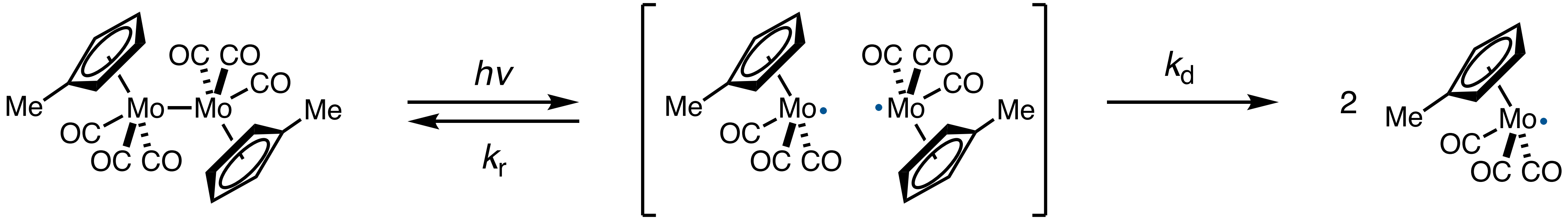
more efficient cage escape

Madsen, D. et al. *J. Phys. Chem. A* **2003**, *107*, 3606–3611.

Thøegensen, J.; Thomsen, C. L.; Poilson, J. A.; Keiding, S. R. *J. Phys. Chem. A* **1998**, *102*, 4186–4191.

Wavelength effects in photodissociation of organometallic complexes

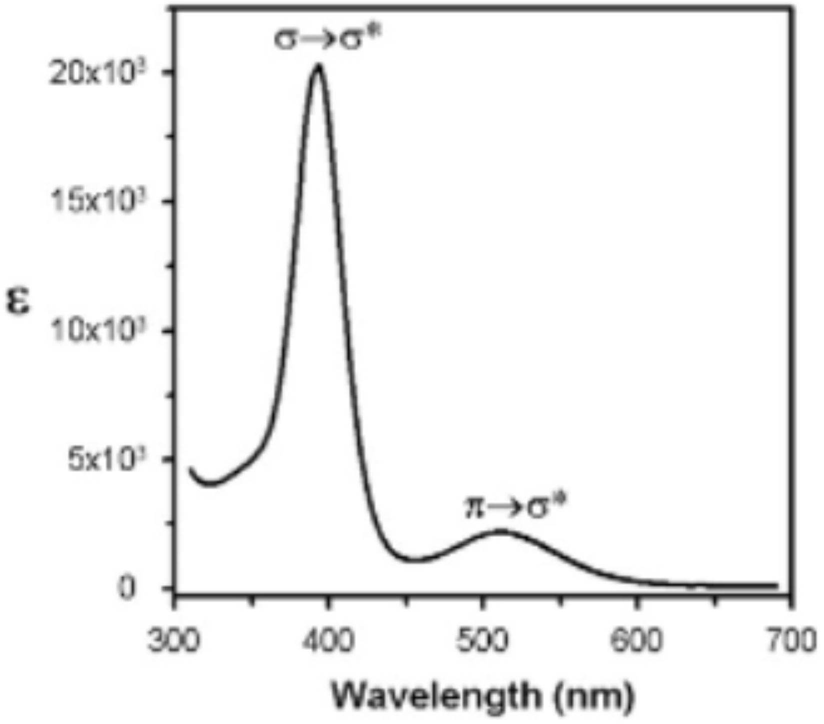
- *Decrease* in cage escape obeserved when irradiating Mo–Mo complexes with shorter-wavelength light



λ (nm)	**F_{cP}**	**transition**
546	0.27 ± 0.02	$\pi \rightarrow \sigma^*$
436	0.42 ± 0.03	$\sigma \rightarrow \sigma^*$
404	0.45 ± 0.05	$\sigma \rightarrow \sigma^*$
366	0.40 ± 0.05	$\sigma \rightarrow \sigma^*$

$$F_{cP} = \frac{k_r}{k_r + k_d}$$

fraction of radicals that react in-cage

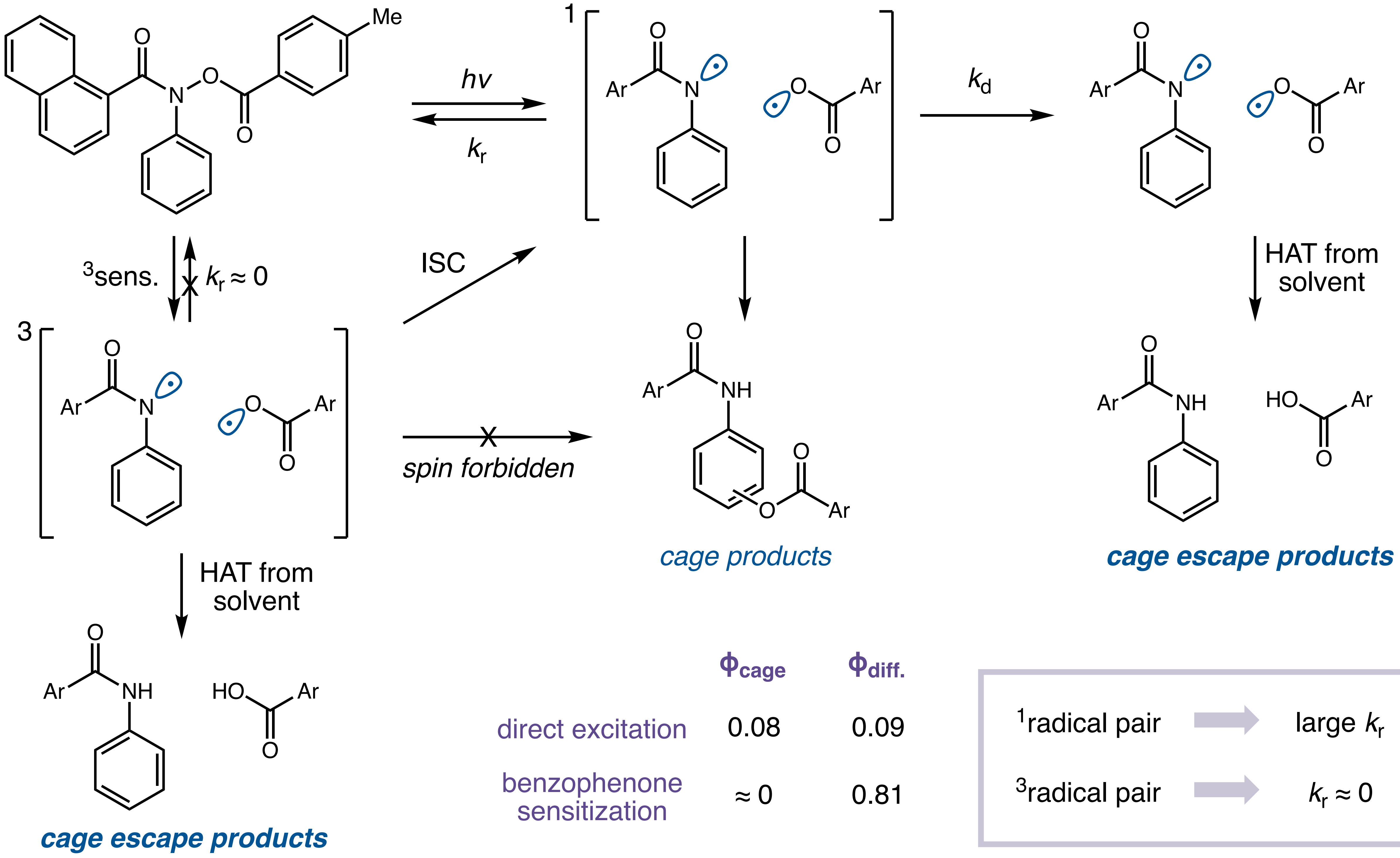


does the excited transition, and not excess energy, determine F_{cP} in this case?

Harris, J. D.; Oelkers, A. B.; Tyler, D. R. *J. Organomet. Chem.* **2007**, *692*, 3261–3266.

Does radical spin state affect cage efficiency?

- Different results observed via direct excitation and sensitization



	Φ_{cage}	$\Phi_{diff.}$
direct excitation	0.08	0.09
benzophenone sensitization	≈ 0	0.81

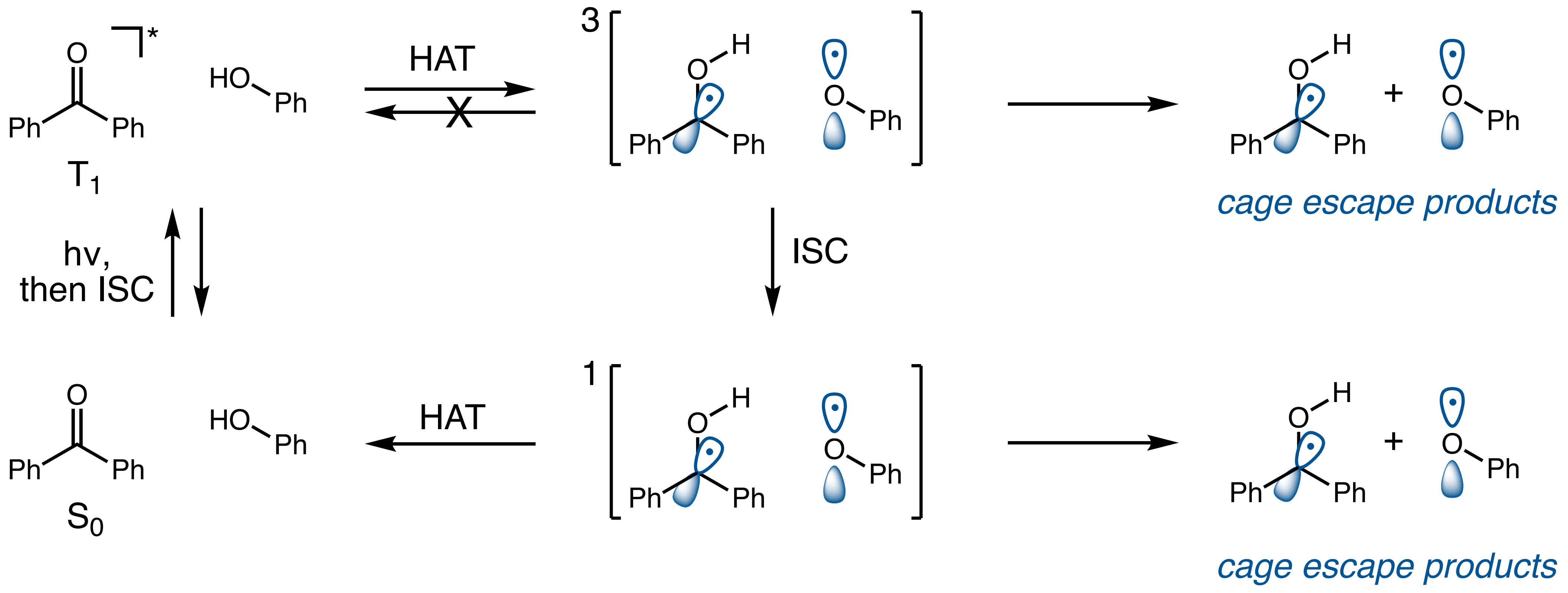
^{1}radical pair ⇨ large k_r

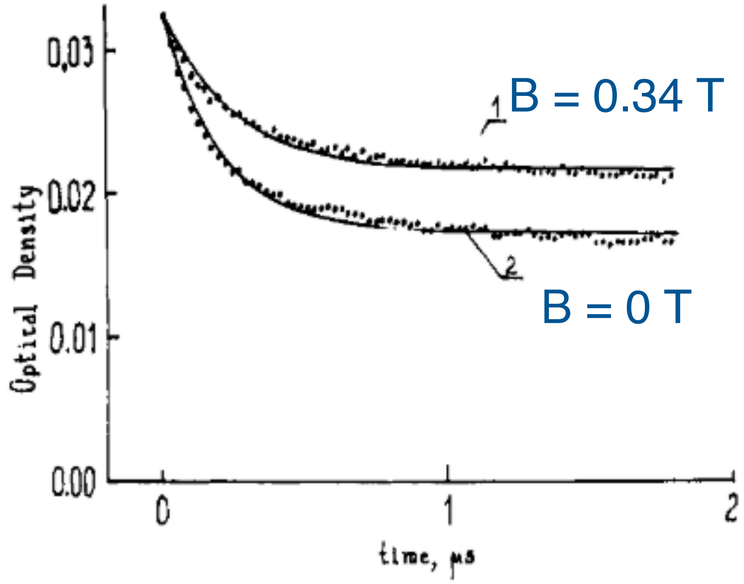
^{3}radical pair ⇨ $k_r \approx 0$

Tadamitsu, S.; Hidenori, S.; Hiroyasu, I. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2875–2881.

Cage effects in benzophenone HAT

- Magnetic field effects reveal role of intersystem crossing in cage recombination





B (T)	**F_{cP}**
0.34	0.34
0	0.47

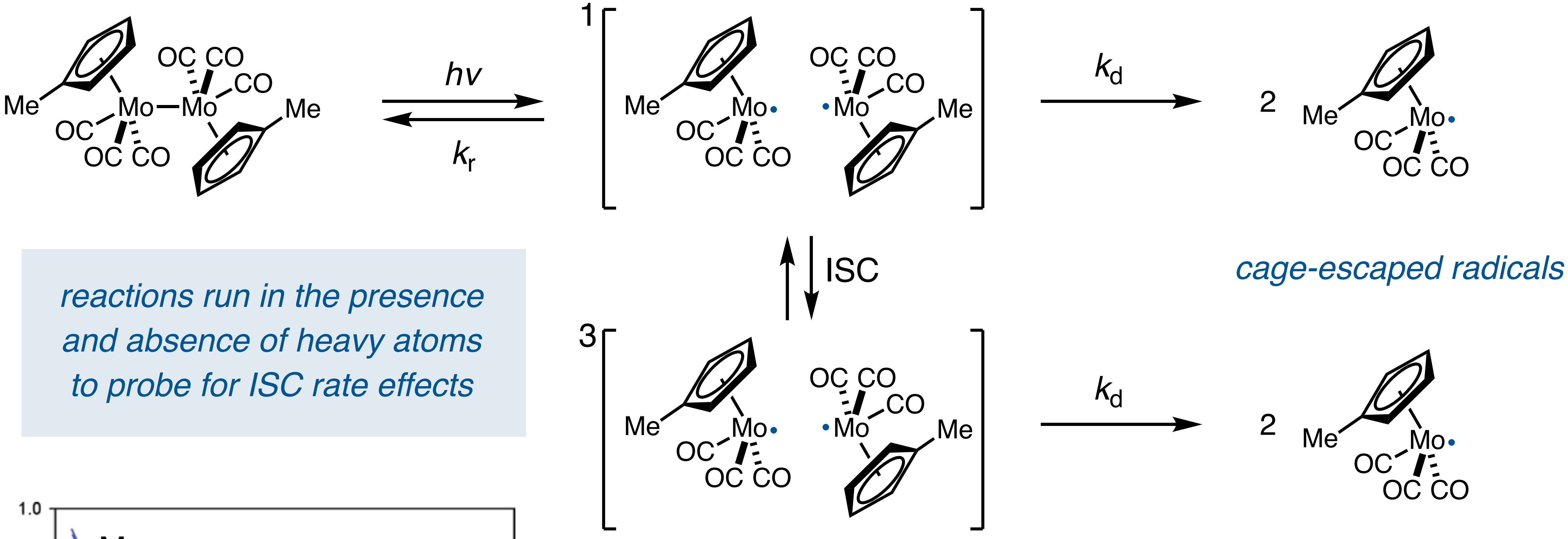
$$F_{cP} = \frac{k_r}{k_r + k_d}$$

fraction of radicals that react in-cage

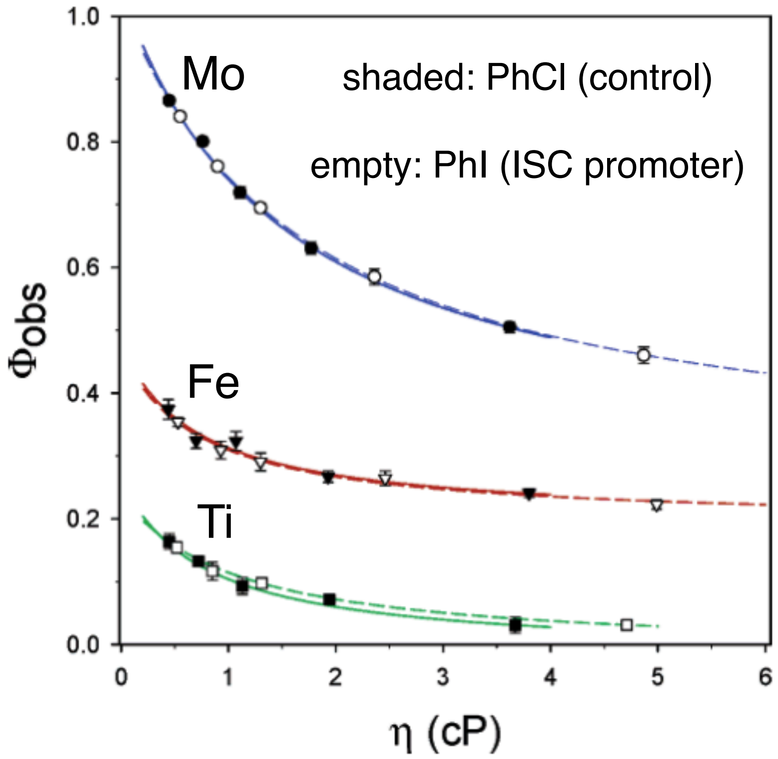
Levin, P. P.; Khudyakov, I. V.; Kuzmin, V. A. *J. Phys. Chem.* **1989**, *93*, 208–214.

Spin barriers in recombination of transition metal radicals

- Lack of heavy atom effects suggest that there is no spin barrier to transition metal radical recombination



reactions run in the presence and absence of heavy atoms to probe for ISC rate effects



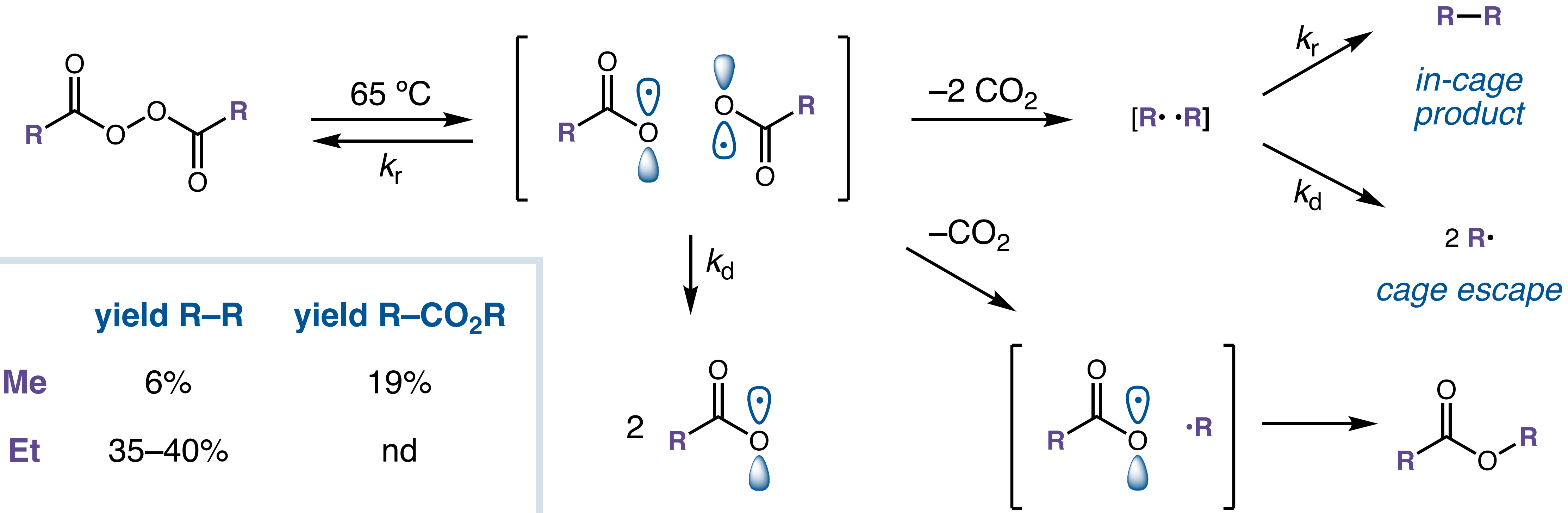
heavy atoms have no effect on radical cage efficiency

there is no significant spin barrier to recombination

Harris, J. D.; Oelkers, A. B.; Tyler, D. R. *J. Am. Chem. Soc.* **2007**, *129*, 6255–6262.

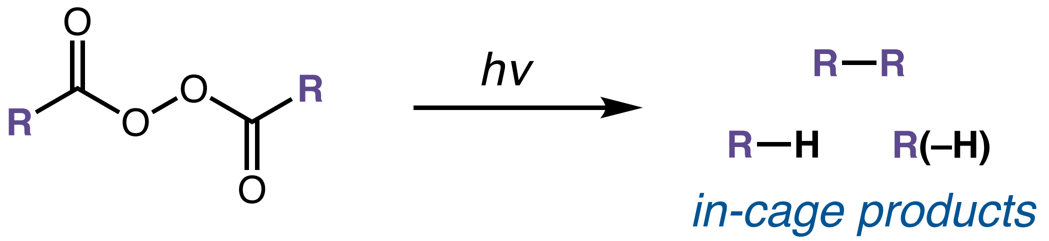
Effect of radical size on cage effects

- Propionyl peroxide shows much higher cage efficiency than acetyl peroxide



	yield R–R	yield $R–CO_2R$
Me	6%	19%
Et	35–40%	nd

- Similar trend not observed under photochemical conditions



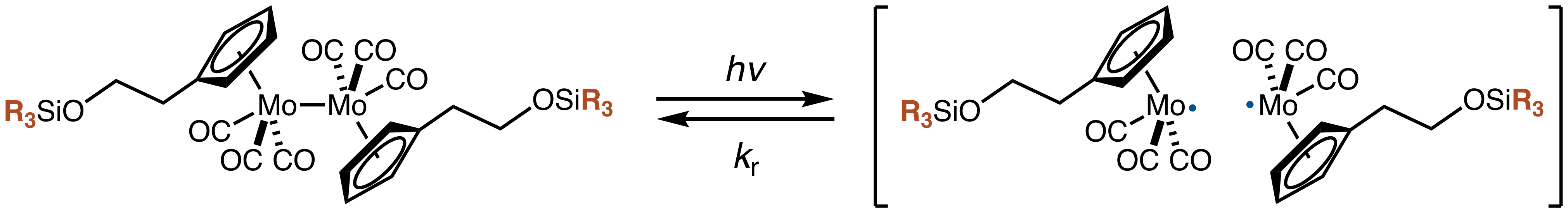
	Et	Pr	Bu	*i*-Pr	*i*-Bu
%cage reaction	**55**	**57**	**51**	**54**	**57**

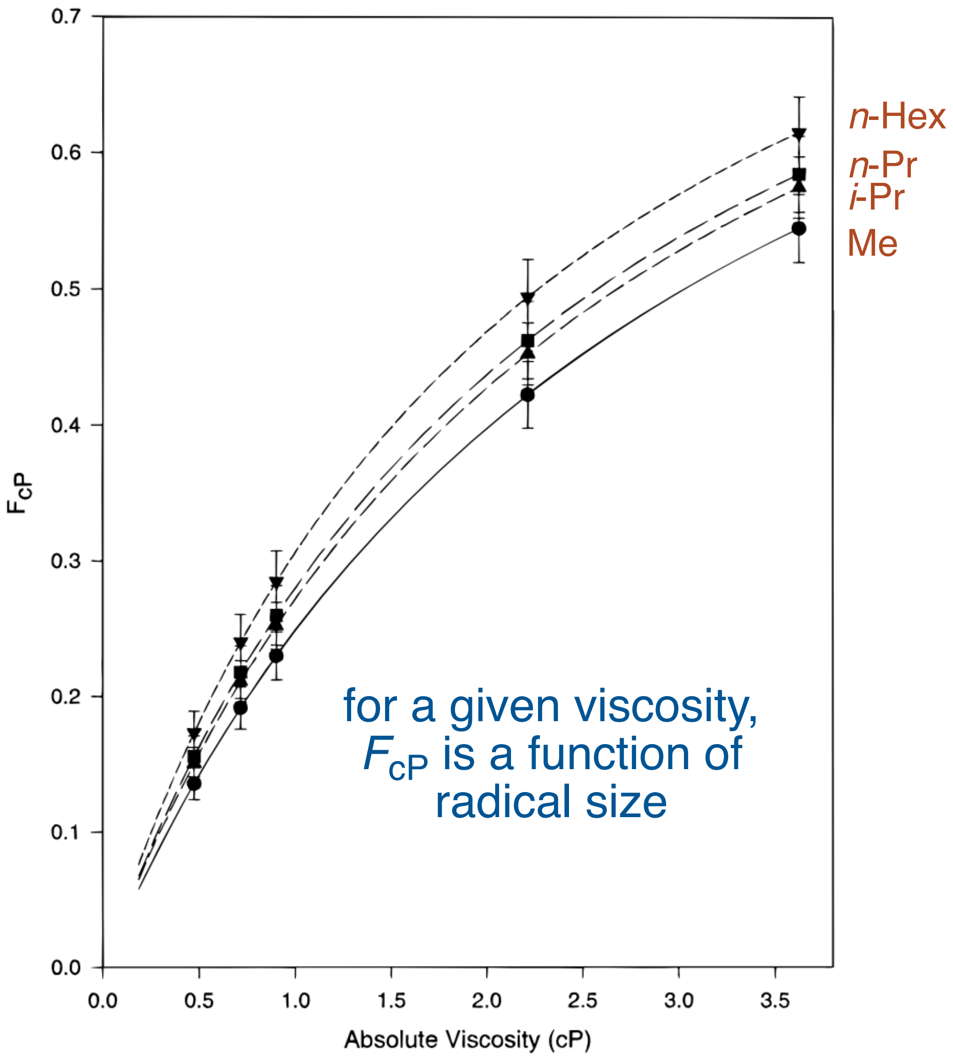
no effect of R on cage efficiency

Herk, L.; Feld, M.; Swarc, M. *J. Am. Chem. Soc.* **1961**, *83*, 2998–3005.
Sheldon, R. A.; Kochi, J. *J. Am. Chem. Soc.* **1970**, *92*, 4395–4404.

Systematic study of radical size in organometallic radicals

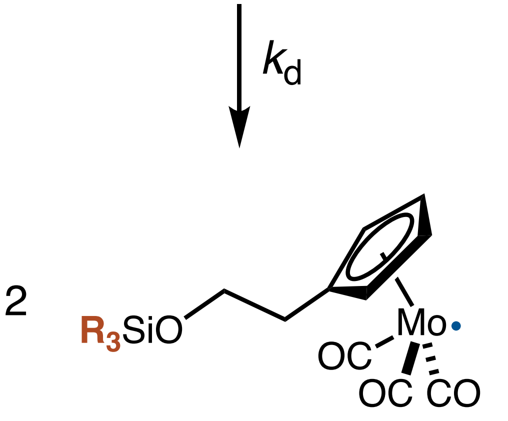
- Clear dependence observed between silyl substituent and cage efficiency





for a given viscosity, F_{cP} is a function of radical size

Figure 2. Plot of F_{cP} vs viscosity for $(R_3SiOCH_2CH_2Cp)_2Mo_2(CO)_6$ [R = Me (●), *i*-Pr (▲), *n*-Pr (■), *n*-Hx (▼)] with CCl_4 (2 M) at 23 ± 1 °C in hexane/mineral oil. All error bars represent ±1 σ.



all free radicals quenched by CCl_4

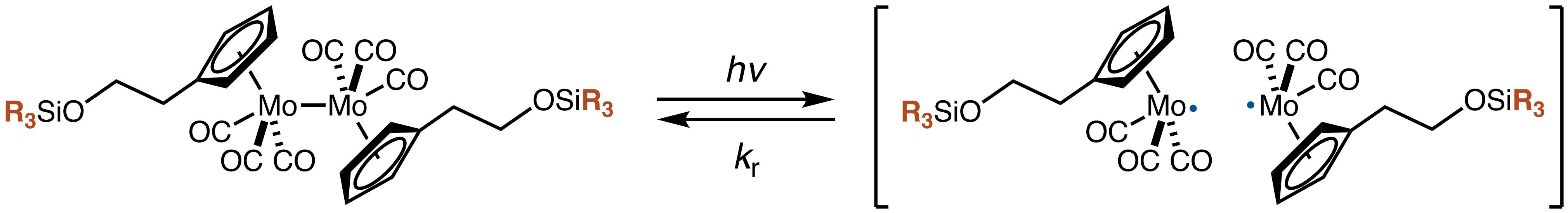
$$F_{cP} = \frac{k_r}{k_r + k_d}$$

fraction of radicals that react in-cage

Male, J. L.; Lindfors, B. E.; Covert, K. J.; Tyler, D. R. *J. Am. Chem. Soc.* **1998**, *120*, 13176–13186.

Systematic study of radical size in organometallic radicals

- Observed linear plot of $m^{1/2}/r^2$ consistent with Noyes original model



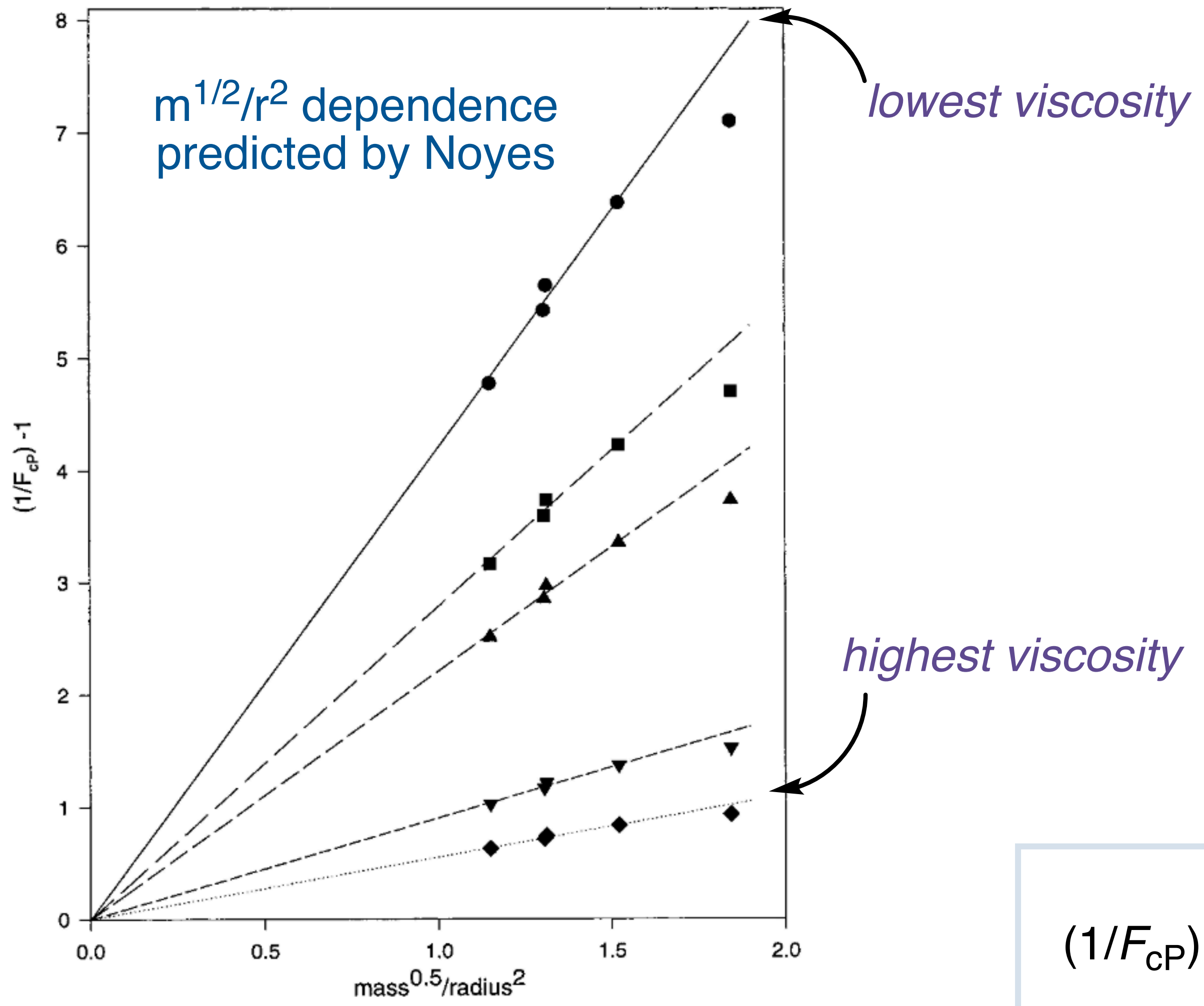
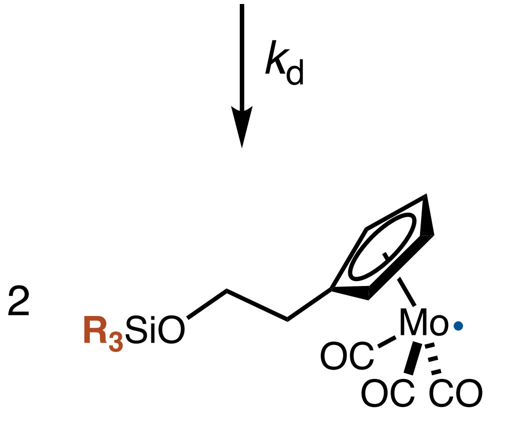


Figure 3. Plot of $F_{cP}^{-1}-1$ vs $m^{1/2}/r^2$ (m = mass of the radical; r = the radius of a sphere with the same volume as the static volume of the radical) for $(R_3SiOCH_2CH_2Cp)_2Mo_2(CO)_6$ (R = Me, *i*-Pr, *n*-Pr, *n*-Hx) and $(MeCp)_2Mo_2(CO)_6$ (in this order left to right) at the measured viscosities of: 0.47 (●), 0.72 (■), 0.90 (▲), 2.2 (▼), 3.6 (◆) cP.



all free radicals quenched by CCl_4

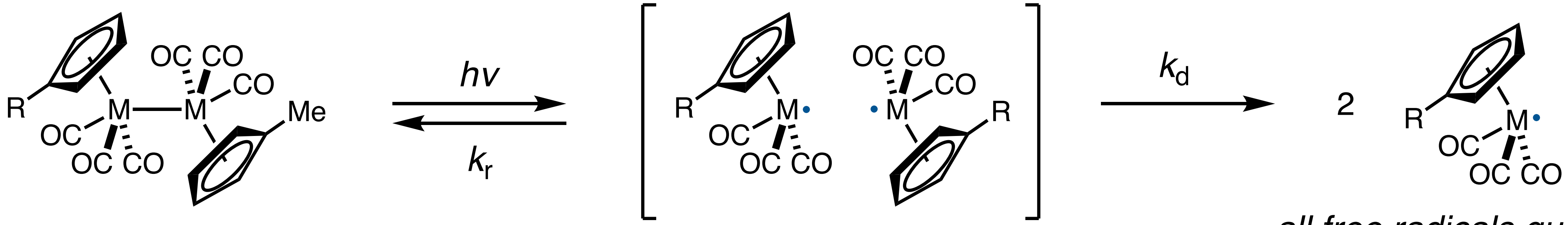
$$(1/F_{cP}) - 1 = \frac{k_d}{k_r}$$

ratio of diffusion to recombination

Male, J. L.; Lindfors, B. E.; Covert, K. J.; Tyler, D. R. *J. Am. Chem. Soc.* **1998**, *120*, 13176–13186.

Systematic study of radical size in organometallic radicals

- Results with M = W show significant variation from predicted $m^{1/2}/r^2$ relationship



all free radicals quenched by CCl_4

	***M* (g/mol)**	***r* (kcal/mol)**	**$m^{1/2}/r^2$**
M = Mo, R = Me	259.1	2.95	1.85
M = Mo, R = $Me_3SiOCH_2CH_2$–	361.3	3.53	1.53
M = W, R = Me	347.0	2.95	2.14

higher $m^{1/2}/r^2$ predicts more cage escape, lower F_{cP}, but W compound shows high F_{cP}

$D_{W–W} \approx 56$ kcal/mol; $D_{Mo–Mo} \approx 32$ kcal/mol

reduced exothermicity prevents cage escape?

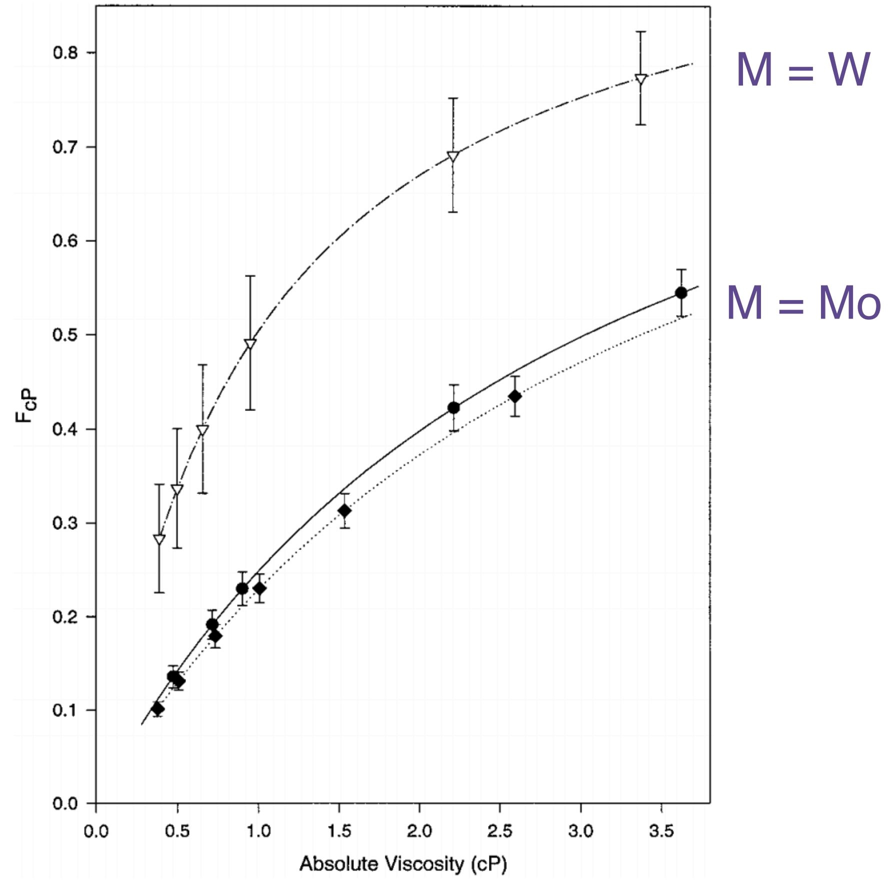
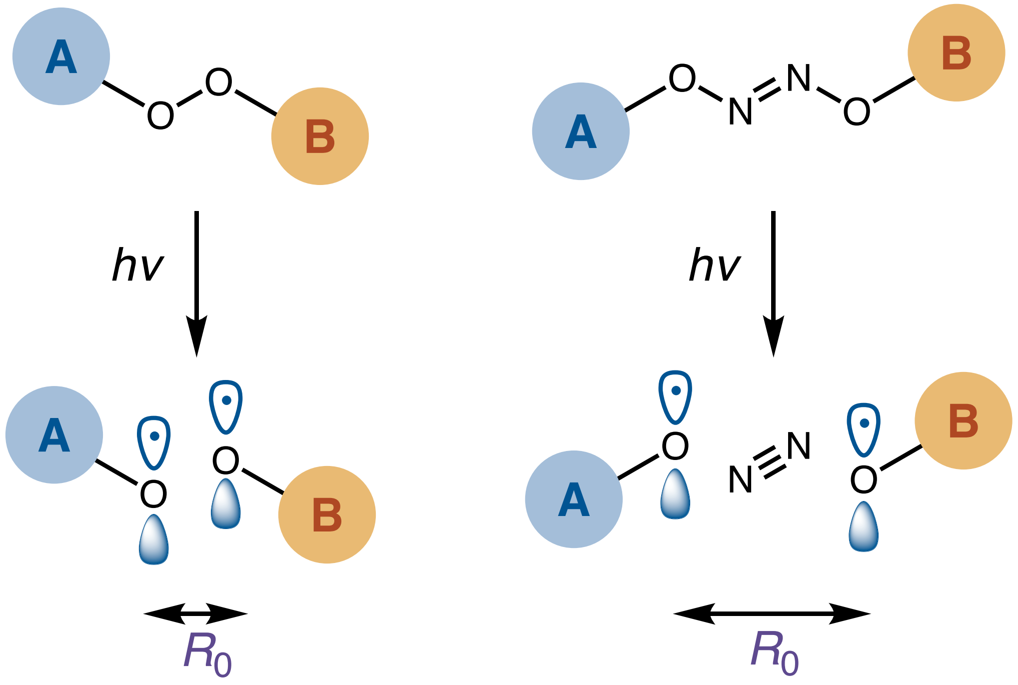


Figure 6. Plot of F_{cP} vs viscosity for the $(Me_3SiOCH_2CH_2Cp)_2Mo_2(CO)_6$ (●), $(MeCp)_2Mo_2(CO)_6$ (◆), $(MeCp)_2W_2(CO)_6$ (▽) molecules with CCl_4 (2 M) in hexane/mineral oil at 23 ± 1 °C. All error bars represent ±1 σ.

Male, J. L.; Lindfors, B. E.; Covert, K. J.; Tyler, D. R. *J. Am. Chem. Soc.* **1998**, *120*, 13176–13186.

Effects of spacer length on cage recombination

- Different spacers generate radicals at different initial distances



initial separation of radicals

$$F = \left(\frac{R_0 - 2b}{2b}\right) + \left(\frac{R_0}{2b}\right)\left[\left(\frac{A_T + \alpha A_E}{\alpha}\right)\left(\frac{1}{\eta}\right) + \left(\frac{A_T \cdot A_E}{\alpha}\right)\left(\frac{1}{\eta}\right)^2\right]$$

F = [1/(fraction of radicals that react in-cage)] – 1

Noyes equation predicts probability of cage escape is a function of initial distance between radicals

- Diffusion of spacer occurs on the order of diffusion of generated radicals

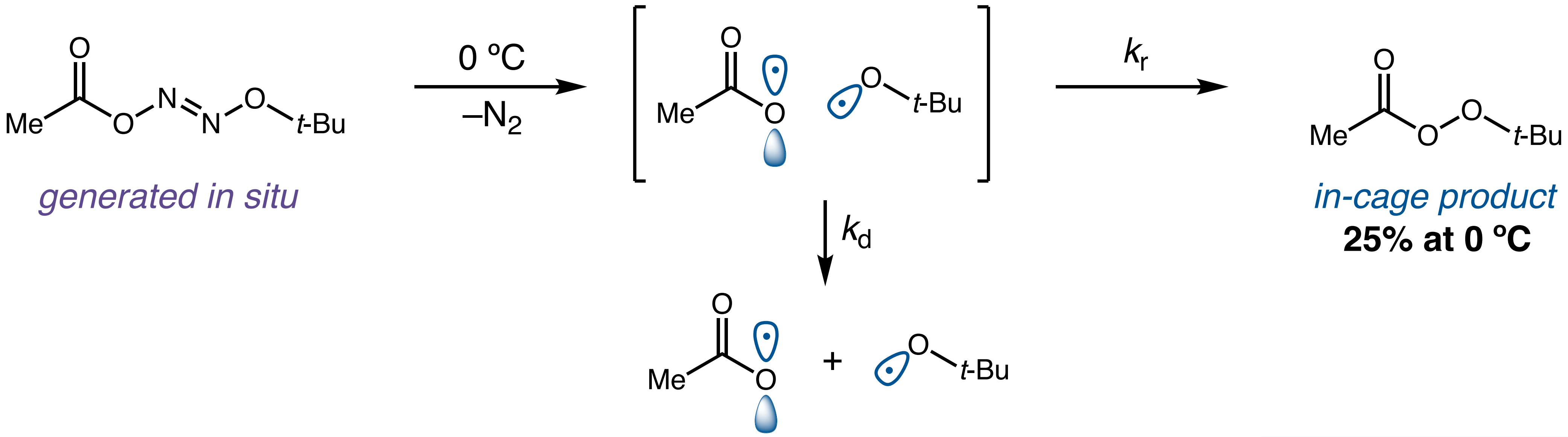
	CO_2	**N_2**	**CyH**	**PhMe**
$D \cdot 10^9$ (m^2/s), in H_2O	1.99	2.19	0.84	0.85
$D \cdot 10^9$ (m^2/s), in CCl_4	3.20	3.60	1.22	1.50

complicates interpretation of experiments based on extrusion of gaseous spacers

Koenig, T.; Fischer, H. “Cage” Effects. In *Free Radicals*; Kochi, J., Ed.; Wiley: New York, 1973; Vol. 1; pp 171–174.
Braden, D. A.; Parrack, E. E.; Tyler, D. R. *Coord. Chem. Rev.* **2001**, *211*, 279–294.

Generation of same radical pair via two different precursors

- Significant differences in cage effects concluded



generated in situ

in-cage product
25% at 0 °C

radical pair generation	**calculation method**	**F_c (100 °C)**
generated via hyponitrite	*extrapolation based on viscosity*	***0.05***

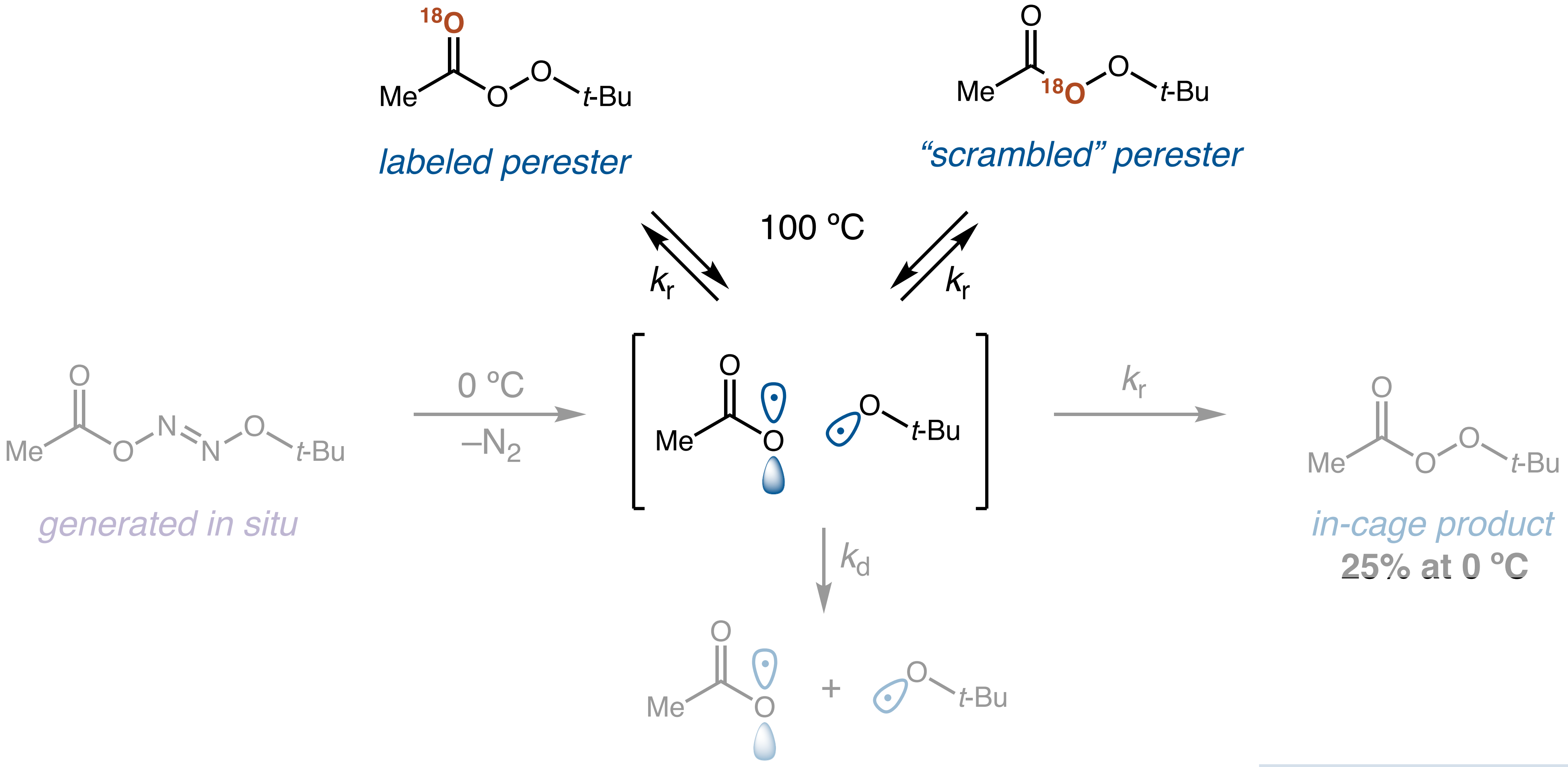
$$F_c = \frac{k_r}{k_r + k_d}$$

fraction of radicals that react in-cage

Koenig, T.; Deinzer, M. *J. Am. Chem. Soc.* **1968**, *90*, 7014–7019.

Generation of same radical pair via two different precursors

- Significant differences in cage effects concluded



radical pair generation	**calculation method**	**F_c (100 °C)**
generated via hyponitrite	*extrapolation based on viscosity*	***0.05***
generated via perester	*comparison of scrambling to consumption of perester*	***0.40***

$$F_c = \frac{k_r}{k_r + k_d}$$

fraction of radicals that react in-cage

Koenig, T.; Deinzer, M. *J. Am. Chem. Soc.* **1968**, *90*, 7014–7019.

Outline

- **Introduction to cage effects**
    - *General definition, theoretical predictions*

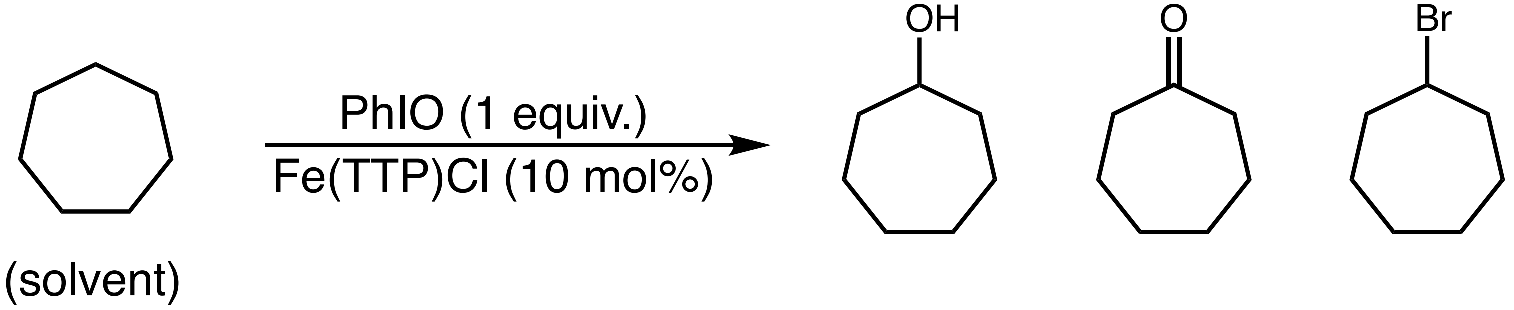
- **Experimental support for the existence of cage effects**
    - *Quantum yields, product ratios as a function of reaction medium*

- **Parameters determining the magnitude of cage effects**
    - *Viscosity, reaction energetics, spin state, radical size, initial separation*

- **Recent case studies**
    - *Presence in biorelevant systems, transient absorption studies*

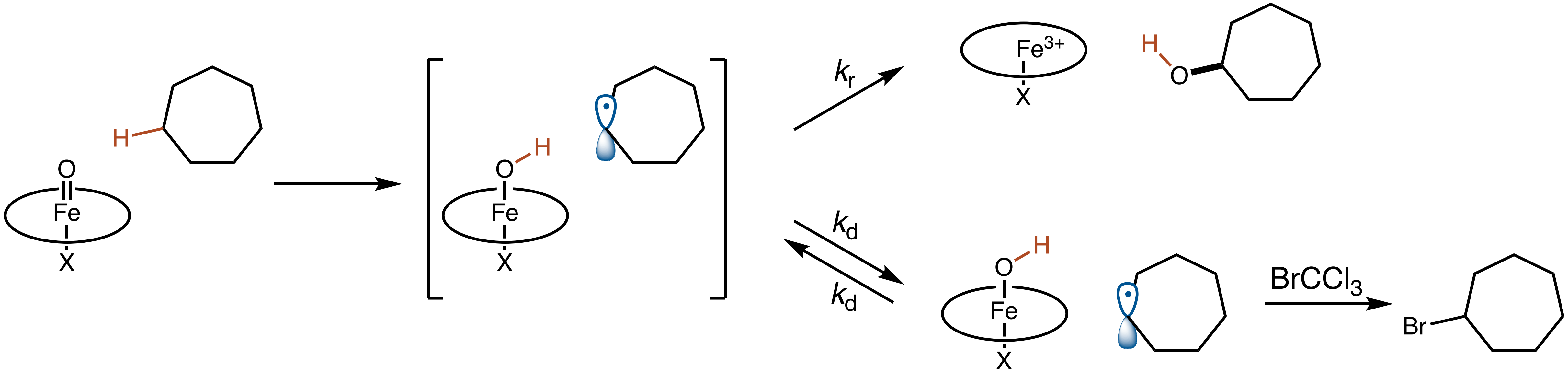
Cage effects in iron porphyrin oxidation

- Reaction in the presence of scavenger suggests both cage and non-cage processes



without $BrCCl_3$	31%	6%	na
with $BrCCl_3$ (20 equiv.)	24%	3.6%	18%

yield in the presence of scavenger supports in-cage recombination

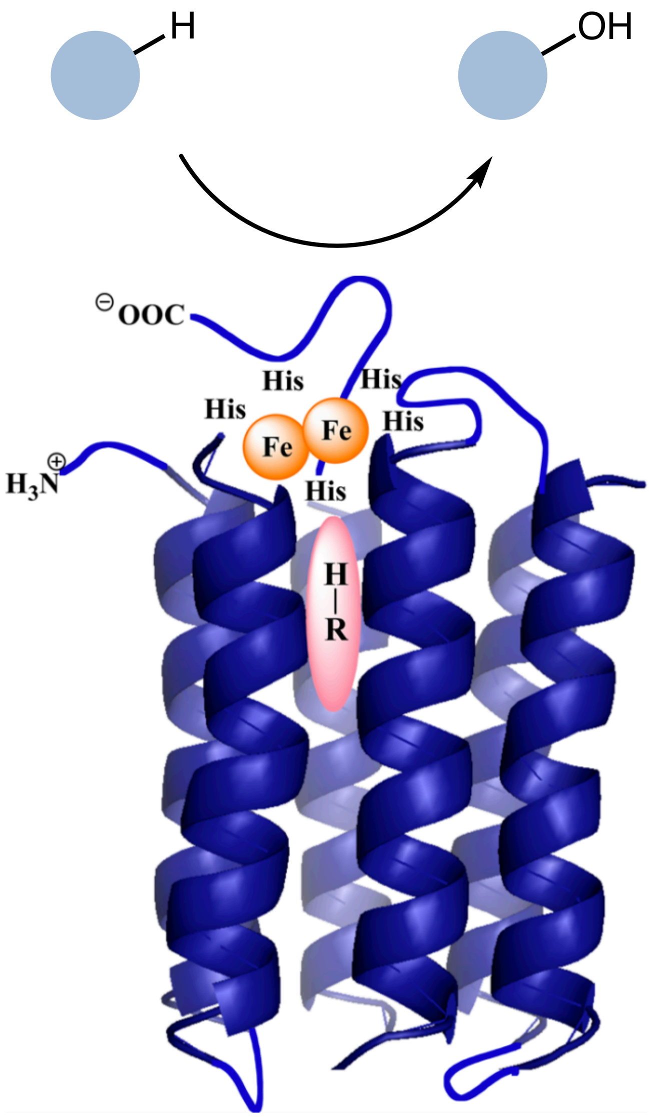


free radicals

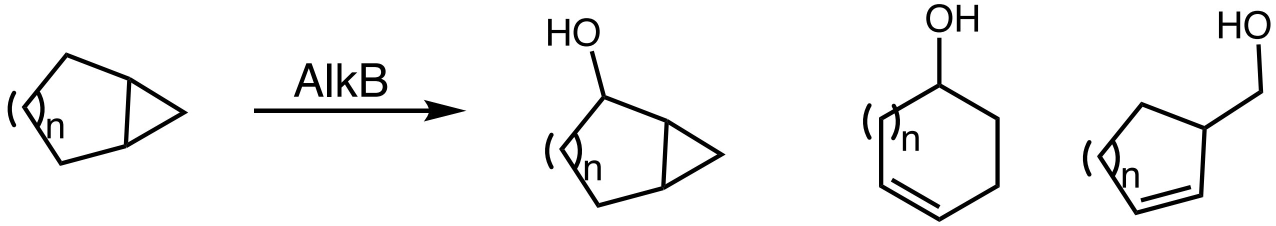
Groves, J. T.; Huang, X. *J. Biol. Inorg. Chem.* **2017**, *22*, 185–207.
Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243–6248.

Cage effect confounds radical clock studies of AlkB

- A range of cyclopropane radical clocks give vastly different lifetimes for the alkyl radical

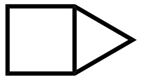
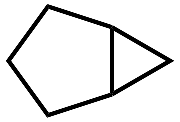
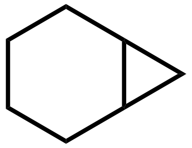


AlkB



*unrearranged product (**U**)*

*rearranged products (**R**)*

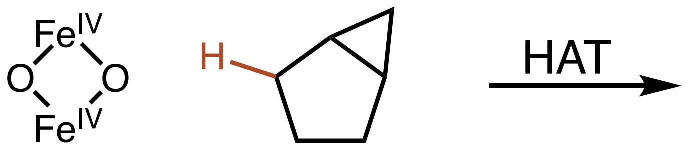
	R/U	***k*$_{\text{rearr}}$ (s^{-1})**	**τ (ns)**
	1.6	2.0×10^9	0.78
	4.7	2.8×10^7	7.8
	1.6	2.0×10^8	170

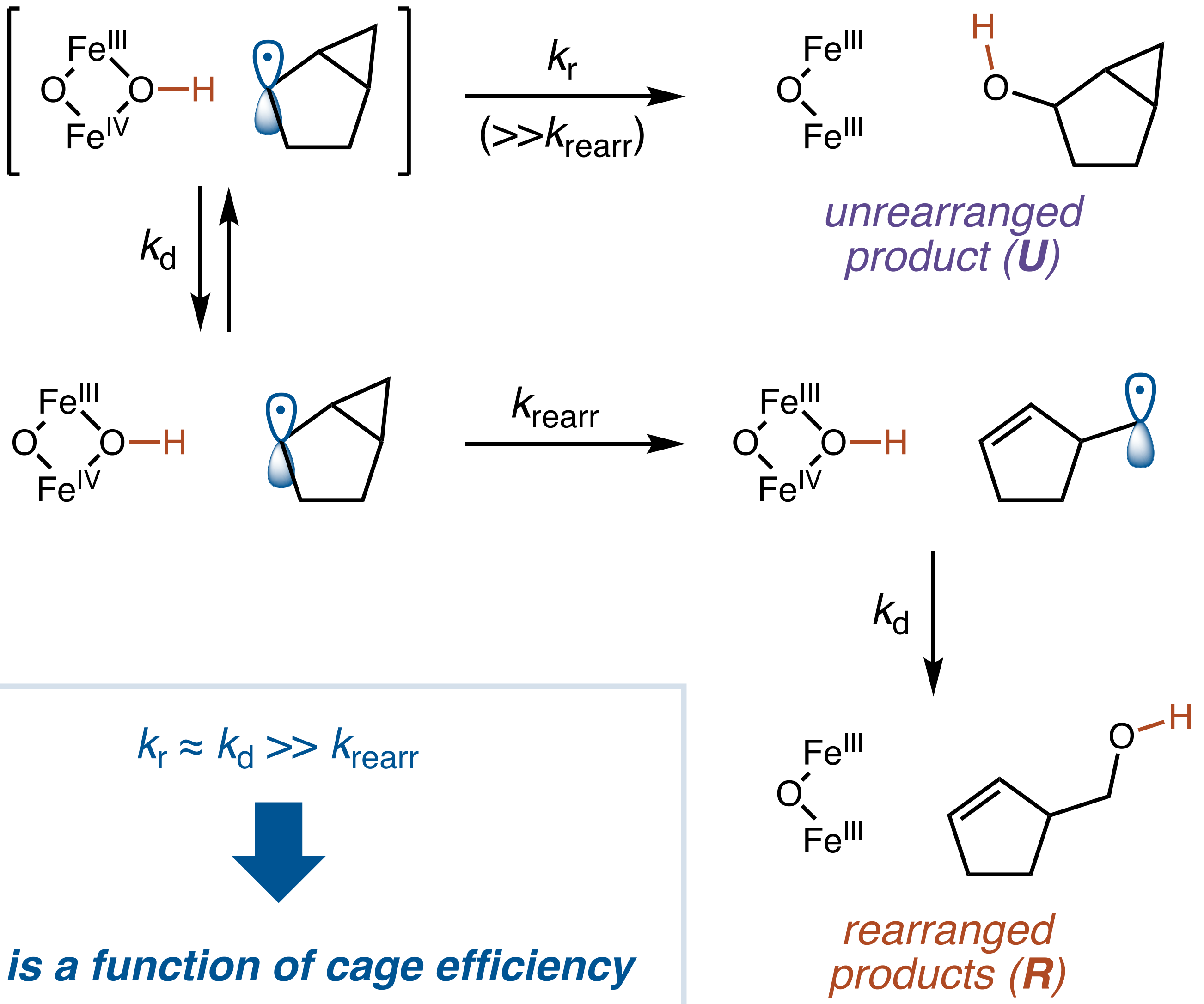
why do different radical clocks give different lifetimes?

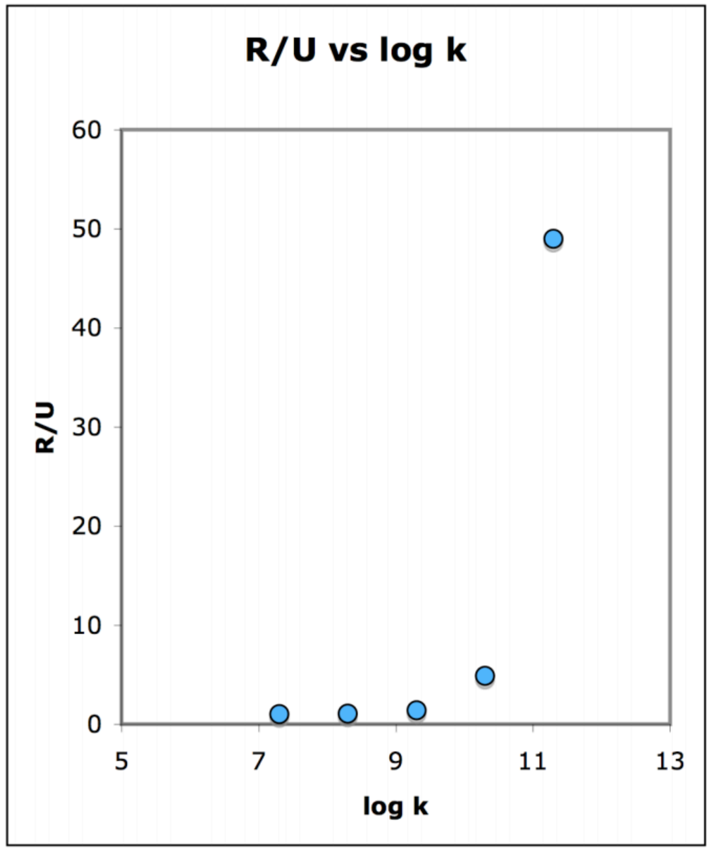
Groves, J. T.; Huang, X. *J. Biol. Inorg. Chem.* **2017**, *22*, 185–207.
Austin, R. N. et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 5232–5234.

Similar rates of cage escape and recombination alter rearranged vs. unrearranged

- Similar rates of recombination and diffusion complicate interpretation of radical clocks







for $k_r \approx k_d = 5 \times 10^9$

$k_r \approx k_d >> k_{rearr}$

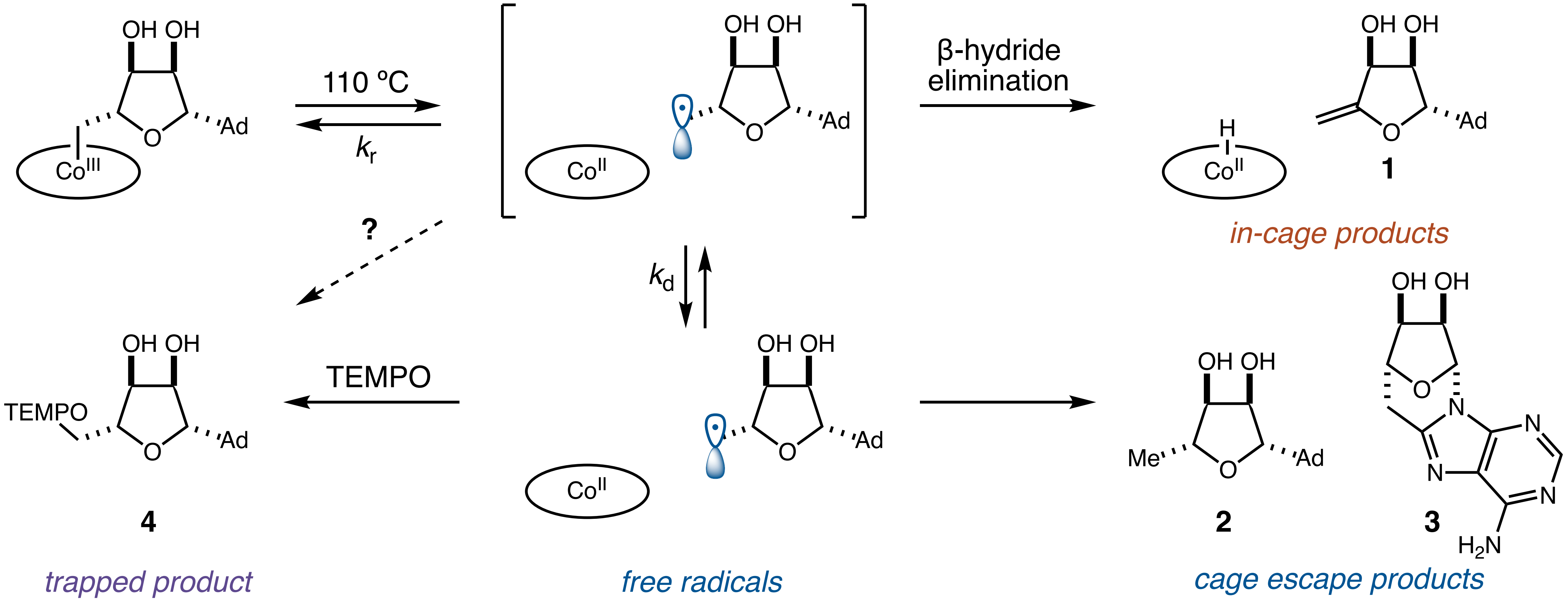
R:U is a function of cage efficiency

for $k_r \approx k_d = 5 \times 10^9$, model predicts R/U ≈ 1 for $10^7 < k_{rearr} < 10^{10}$

Groves, J. T.; Huang, X. *J. Biol. Inorg. Chem.* **2017**, *22*, 185–207.
Austin, R. N. et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 5232–5234.

Cage effects in the chemistry of coenzyme B_{12}

- "Base off" analogue of B_{12} shows significant in-cage recombination in ethylene glycol



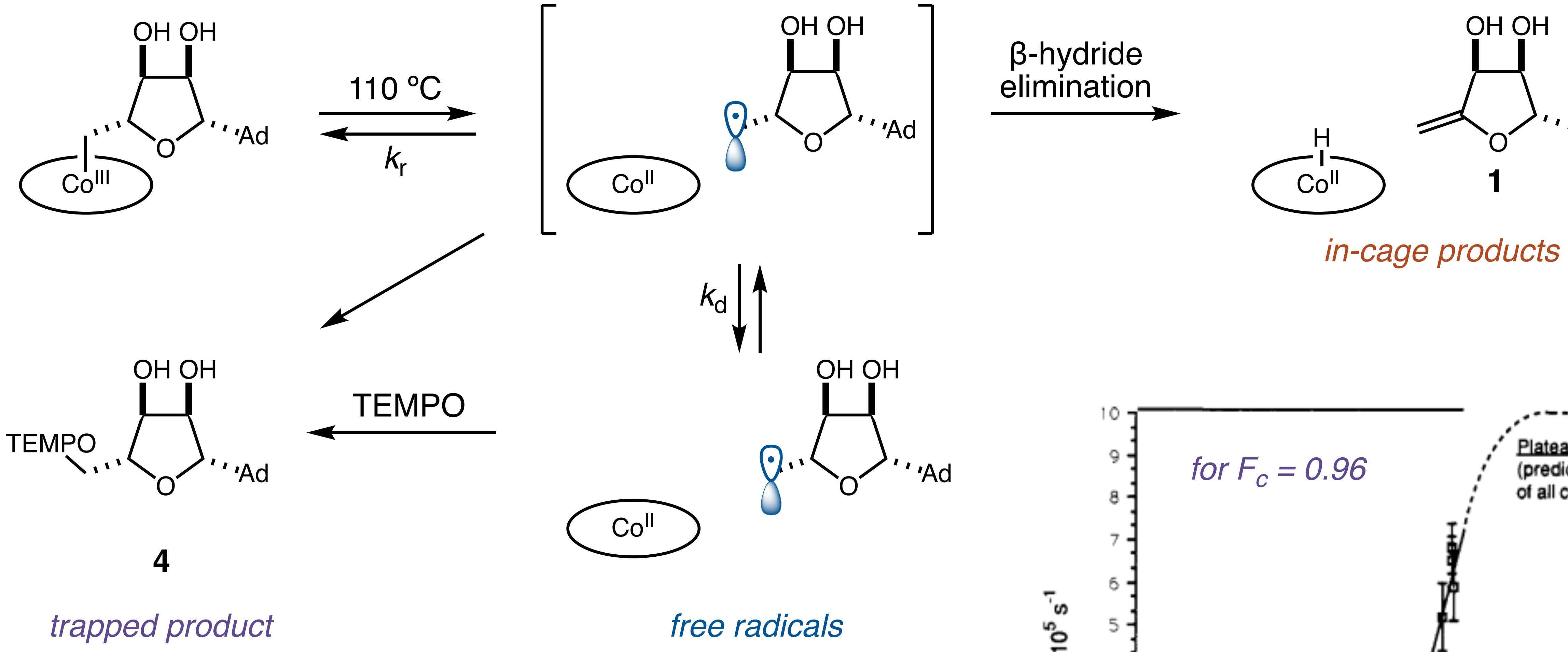
[TEMPO]	β–hydride (**1**)	HAT (**2**)	Minisci (**3**)	TEMPO (**4**)
0	33%	45%	15%	0
0.12 M	24%	1%	0%	73%
0.75 M	9%	0%	0%	89%
0.85 M	7%	0%	0%	91%

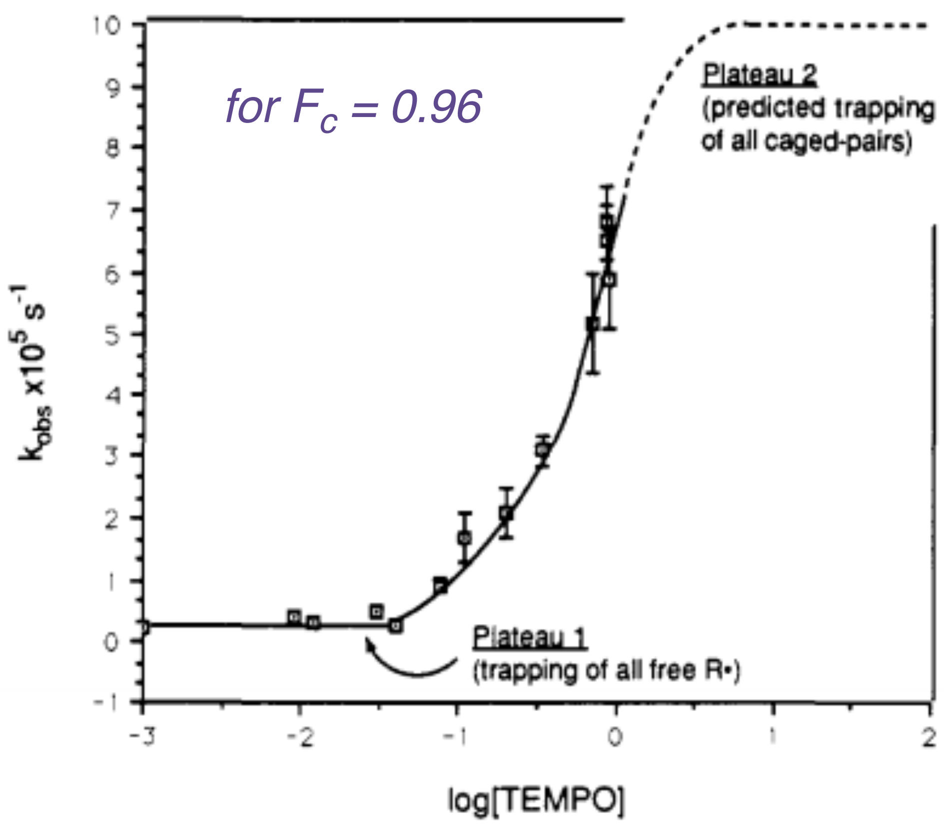
inhibition of β-hydride by TEMPO supports stepwise mechanism

Garr, C. D.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 10440–10445.

Cage effects in the chemistry of coenzyme B_{12}

- Kinetic dependence of starting material disappearance on TEMPO supports in-cage trapping





Is TEMPO trapping the primary or secondary radical pair?

Garr, C. D.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 10440–10445.

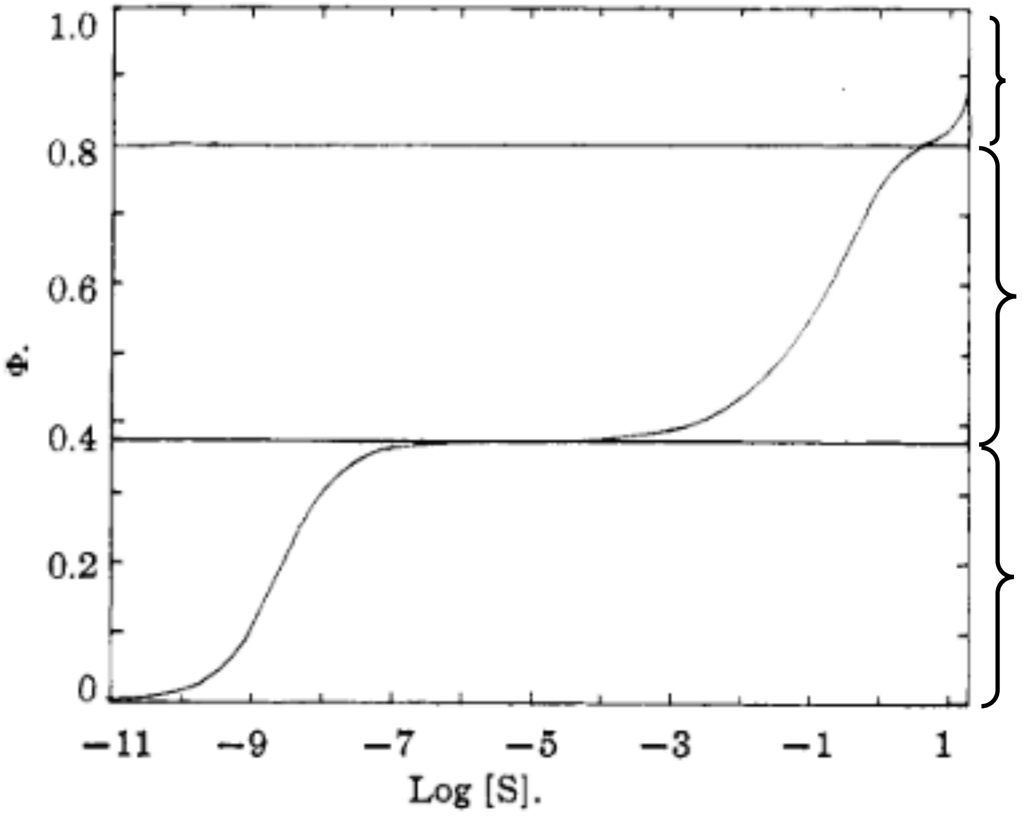
Experimental support for secondary cage effects

- Early theoretical studies predict significant kinetic importance of primary and secondary cage effects

$$\mathrm{A{-}B} \underset{k_\mathrm{r}}{\overset{h\nu}{\rightleftarrows}} [\mathrm{A}\cdot\ \cdot\mathrm{B}] \underset{k_\mathrm{d}}{\overset{k_\mathrm{d}}{\rightleftarrows}} [\mathrm{A}\cdot\ |\ \cdot\mathrm{B}] \xrightarrow{k_\mathrm{d}} \mathrm{A}\cdot + \mathrm{B}\cdot$$

primary cage *secondary cage* *free radicals*

Φ vs. [radical scavenger]



some primary cage quenching observed

free radicals + secondary cage quenched

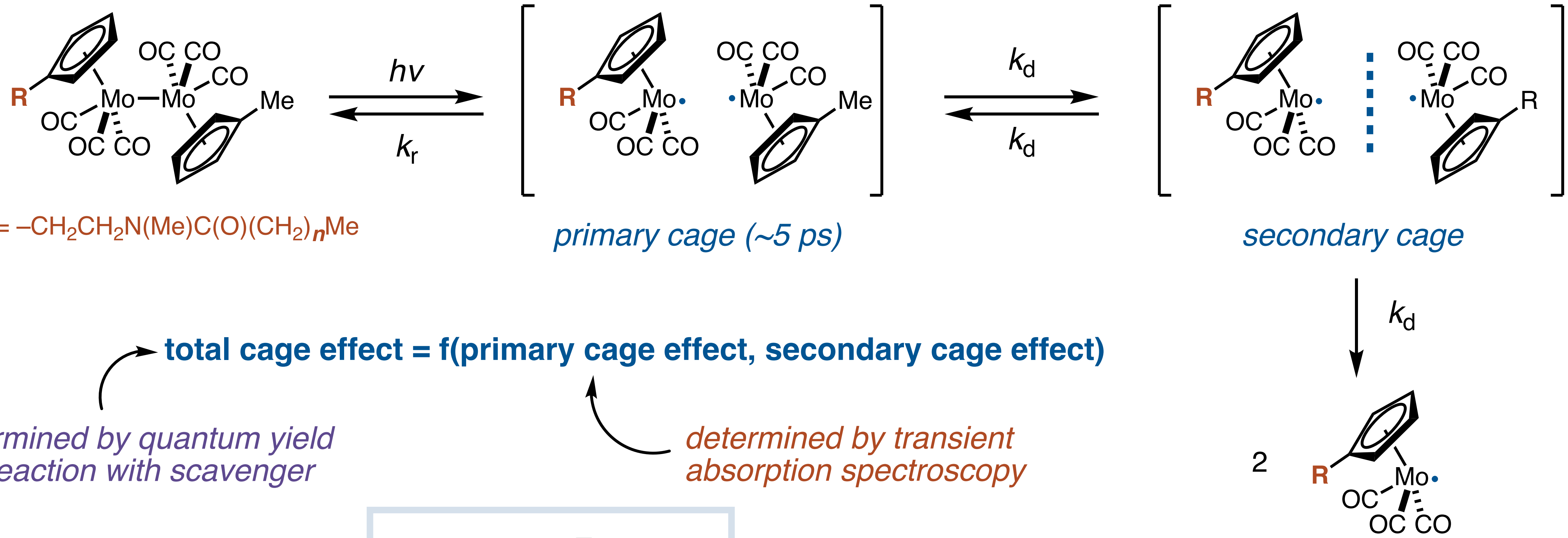
only free radicals quenched

experimental techniques generally only provide the total cage effect

Noyes, R. M. *J. Am. Chem. Soc.* **1955**, *77*, 2042–2045.

Combined approach enables separation of primary and secondary effects

- Mathematical treatment enables determination of secondary cage effect from primary and total cage effects



R = $–CH_2CH_2N(Me)C(O)(CH_2)_nMe$

primary cage (~5 ps)

secondary cage

free radicals

total cage effect = f(primary cage effect, secondary cage effect)

determined by quantum yield of reaction with scavenger

determined by transient absorption spectroscopy

$$F_{cP} = \frac{F_{c1}}{1 - F_{c2}(1 - F_{c1})}$$

ligand	total cage effect	primary	secondary
$n = 3$	0.42 ± 0.03	0.42 ± 0.02	0
$n = 8$	0.48 ± 0.03	0.42 ± 0.03	0.22
$n = 13$	0.59 ± 0.04	0.44 ± 0.01	0.45
$n = 18$	0.70 ± 0.04	0.43 ± 0.02	0.68

secondary cage effects account for difference in cage efficiency as a function of molecular size

Oelkers, A. B.; Tyler, D. R. *Photochem. Photobiol. Sci.* **2008**, *7*, 1389–1390.

Outline

- **Introduction to cage effects**
  - *General definition, theoretical predictions*
- **Experimental support for the existence of cage effects**
  - *Quantum yields, product ratios as a function of reaction medium*
- **Parameters determining the magnitude of cage effects**
  - *Viscosity, reaction energetics, spin state, radical size, initial separation*
- **Recent case studies**
  - *Presence in biorelevant systems, transient absorption studies*

Radical cage effect

radical cage effect:

increased likelihood that diffusive separation will be slower than radical pair recombination in solution

↓

broadly observed in synthetically relevant radical reactions, but often ignored

↓

likely plays a significant role in the success or failure of important single-electron transformations